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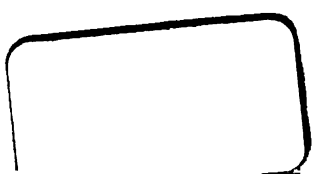

TRANSACTIONS

OF THE

ASSOCIATION OF AMERICAN PHYSICIANS.

ELEVENTH SESSION,

HELD AT WASHINGTON, D. C.,

APRIL 30 AND MAY 1 AND 2, 1896.

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MINUTES

OF THE

ELEVENTH ANNUAL MEETING,

Held in Washington, D. C., April 30, *May* 1 *and* 2, 1896.

The following members were present during the meeting:

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G. Baumgarten.	Hobart A. Hare.	D. W. Prentiss.
Herman Biggs.	I. Minis Hays.	William Pepper.
B. Meade Bolton.	Frederick P. Henry.	T. Mitchell Prudden.
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Samuel C. Busey.	A. Jacobi.	B. K. Rachford.
J. M. DaCosta.	E. G. Janeway.	George B. Shattuck.
Charles L. Dana.	W. W. Johnston.	Wharton Sinkler.
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	Francis H. Williams.	

THURSDAY, APRIL 30TH.—MORNING SESSION.

The President, Dr. A. Jacobi, called the Association to order at 11.05 A. M., and delivered the "President's Address," as follows:

GENTLEMEN: The scrutiny of the programme you have prepared for this meeting of the Association of American Physicians yields an elo-

quent exposition of its scope and aims. The Fellows who are offering their contributions to the discussions of these three days have in the distant parts of the country, each by himself, and unknown to their far-away co-operators, acted the parts of different constituents of an organism. Indeed, whatever conduces to make up internal medicine, from the special biological study of a coccus to the prognosis in a particular disease, from the etiology of a morbid condition to its therapeutics, from the consideration of a local ailment to that of public hygiene, is well represented. Gathering up the apparently detached threads, I therefore find it far from difficult to express in a few words what I consider to be the relation of medicine, such as it is exhibited in this Association and on its programme, to medicine as it is taught and practised, either undivided or in its specializations, and of this Association to its National sister societies.

At a time when a number of national special organizations had been in existence several years, it was founded, I take it, because the leaders felt that the natural tendency to the division of scientific labor should be not checked but guided by a controlling hand, and that the independent position of internal medicine should be demonstrated and vouchsafed.

Since Boerhaave, aye, since Galen, specialties branched off from the original trunk of medicine. The accumulation of experience, the multiplicity of observers, the increasing depth of studies, the perfection of tools and instruments, and the limitation of the capacity of individual practitioners, at one time even the dictates of the Church have from century to century, and lastly, from decade to decade, added to the number of specialties in practice and of specializations in study. Indeed, at the present time, a medical man may do his full duty to his profession, be an expert largely quoted, the first among his peers, and a peer among the first, an authority of the first rank, without having paid the slightest public attention to the demands of social hygiene, or for years seen a single sick bed. On the other hand, there are those most of whose time is spent and efforts exhausted in attending to the sick, both in hospitals and private dwellings. Their observations may be quite as correct as those of the microscopist and experimenter, but they are not so easily proven to be so. In their case it takes, as a rule, a large number of statistical data to establish facts as truths and worthy of acceptance, for, indeed, truth is not so simple as many a proverb will have it. The reason for this is manifest. The object of the microscopist is single, is one, and still mistakes are made; for explanations differ in regard to what has been seen, and corrections and refutations are numerous. That

of the physician is complex, therefore more difficult. His subject is man, and usually man whose physiological functions are disturbed by a pathological process. His work is also more comprehensive, his aim higher than that of a practical specialist who claims to deal with a single organ.

When we look upon modern specialties as they frequently are, not as they ought to be, practised, we have to admit that they suffer from the danger of limiting the view of the practitioner. An isolated organ is the centre of his perspective, and everything not enclosed in his field of vision, which is occupied by the organ of his choice, is doomed to remain insignificant in his estimation. Moreover, the mercantile and mercenary spirit of the end of the century matures occasional eagerness for early reputation and social and financial success. The public is easily impressed by visible manipulations and manual dexterity, and unable to follow or correctly rate the results of unobtrusive and unornamental brainwork. Thus it is, that to establish himself in reputation and standing among laymen, it takes the accomplished physician as many decades as the young specialist years. On the domain of practical medicine, the specialties have gradually encroached. No cavity but has been invaded by the surgeon, no special organ ever so small but what has been appropriated by a specialist. Is it true, however, that medicine becomes more surgical or specialistic? Is it not rather to be demanded that surgery and the rest of the specialties should remain, or more than hitherto, become medical?

It is not given to me to value scientific labor, beyond the personal happiness conveyed to the searcher for truth by the broadening of his mental horizon and by revelations never manifested before, except by the good it does to the race. *Nisi utile est quod faciamus stulta est gloria.*

The researches which have contributed most to the success of all branches of *surgical* medicine are the same that have added to our knowledge of a large number of infectious diseases and benefited both private and public hygiene. That is where the bacteriological hermit, the studious histologist, the bedside practitioner, and the public statesman join hands. That is where medicine proves itself to be the benefactor not only of the individual, but of mankind. Political economy and individual and public hygiene are equally interested in the progress of medicine. When society will have passed beyond the mire of mercenary wire-pulling and bickering, when every man will be a political being in the sense of Aristotle, with the tendencies of the statesman rather than those of the politician, when the welfare of the people and race will be the only aim of enlightened representatives, then the medi-

cal man will be either the legislator or his adviser, and medicine will take the place occupied in remote medieval times, before there were so many churches, by the Church. But to accomplish that end medicine must remain one and indivisible.

Looking over the programmes of the Climatological, Pædiatric, Gynæcological, Neurological Associations, and the rest, you recognize subjects familiar to yourselves. Let them acknowledge their origin, and the ties are no longer severed. Surgical *science* is medicine. Its *art* only is what constitutes the specialist. The methods of surgical diagnosis are medical. The very sources of its practical success are the pharmacological, biological, and histological laboratories. The very best minds of both hemispheres were always anxious to enforce the union of the *disjecta membra*. No science deserves its name unless enlivened by this idea. Imagine, for instance, anthropology to relinquish its throne and acknowledge the independence of its different branches. The collective studies of crania, or of hair, the peculiarities of the Esquimo tribe, the relationship of languages, they are branches of and contributions to science, not sciences. This knowledge of consanguineous unity was the cause of the formation of our triennial Congress. From that point of view this Association, with its annual meetings drawing on, and combining as it does pathological anatomy, histology, bacteriology, chemistry, physics, and all the practical aids offered by the mechanic, the optician, and by all the specialties, whose number leaves nothing to be desired beyond that it might be smaller, and with its constant contact with the interest of the commonwealth, takes the place of the triennial Congress. One of the wisest members, in my opinion, of this Association was once asked by me what he did in a certain case. His answer was: "Among other things, I prescribed a surgeon." One of the leading specialists of the country told me after he had inspected a volume of our *Transactions:* "I know how to operate on an eye, and now and then I succeed in making a good brain diagnosis. After all, however, we do retail work. When I want statesmanship in the profession I look to internal medicine."

Among the constituents of scientific and practical medicine there is one which has not yet succeeded in conquering its legitimate place, viz., therapeutics. Fifty years ago in Vienna, and there its influence was paramount, the interest in man began at the autopsy. It had become, and occasionally still is customary, even with large minds, to scoff at the value of internal therapeutics. The effects of the knife, the actual cautery, the tourniquet, the local applications on the integuments are readily conceded. But the natural difficulties of directing and control-

ling the action of drugs on distant cell conglomerates, either fluid or solid, are often emphasized and exaggerated into alleged impossibilities. That is a mistake, for the merely empirical character of therapeutics, which, after all, has a value of its own, is to a large extent superannuated. The diagnostic methods of Laennec (with whose illustrious name that of Auenbrugger ought always to be thankfully remembered) and of Skoda, and the introduction of the thermometer by Wunderlich, enabled us to prove some of the local or general actions of medicines. The efficacy of local treatment was proven by Hebra in the treatment of scabies, in the very face of the nihilistic school of Vienna. Pravaz's invention, as ingenious as it was simple, facilitated local administrations with tangible and instantaneous effects. The separation of alkaloids, beginning with that of morphine in 1817, strychnine in 1818, caffein in 1819, added to the accuracy of effect and of observation. Experiments with drugs on animals have vastly contributed to the exactness of our medication, though it is true that every newly discovered fact is liable to be accepted or not with the protest that whatever happens *in corpore vili* need not be applicable to man. In that way we are mainly indebted to Wepfer, who worked as early as 1679, to Magendie and his pupil, Claude Bernard, and to the greatest of them all, Karl Ludwig. Nor was it animals alone that were utilized to accomplish accuracy in the application of medicines. Observation of their action when they were given to the well and the sick has vastly increased our knowledge, in spite of the absurd caricatures furnished by that erudite quack, Hahnemann.

Nor has chemistry and pharmacology, which was in due time separated from pharmacy, been idle. The changes undergone by medicinal agents were studied by Mitscherlich, Schmidt, Wormley, Horatio C. Wood, and Schmiedeberg, and the dependence of the effects of medicines upon their chemical structure by Richardson, Brown, and Frazer, with the final result of creating through synthesis new and powerful agents. One of the most promising observations was this, that certain bacteria are capable of immunizing animals against the action of certain poisons, either through the metabolic products of bacteria, or by the very serum alone of such immunized animals. Finally it was found that as the absence or the diseased condition of the thyroid gland caused serious disorders, so some of the latter could be corrected or cured by the administration in different ways of thyroid tissue or its extracts. These very facts, and the results of serum therapy, and the promises of organotherapy in general, which we expect to be fulfilled in the near future, are most hopeful signs. We are, therefore, amply justified in believing

that internal medicine will soon reap many of the fruits, thus far harvested by external medicine, from the fields of biological and bacteriological laboratory work.

This is more than hope. It is the more a certainty the more surely and frequently physiological and pathological functions are shown to be chemical. Bacteriology, advanced as it is beyond tentative beginnings and the overbearing claims of youthfulness, does no longer pretend to cover the field of etiology. It recognizes the difference between the entity of a disease and its cause. All organic changes in the cells and protoplasm are either physical or chemical, or both. Bacteria cause local infection, usually primary, rarely metastatic in character, but never the constitutional symptoms of a disease. These are produced either by proteins or toxins, the products of the very microbic bodies, or ptomaïnes, the products of the cells in which the presence of microbes worked an abnormal metamorphosis. The latter, however, does not result from bacteric influence only. Chemical, mechanical, thermic changes are apt to influence the normal vital processes, which again impress, or are impressed by, the peculiar individual disposition created by age, hereditary influence, previous illness, state of nutrition, nerve-force, and the conditions of rest or exhaustion. What a wonderful and complicated chain of mutual influences and possibilities, and what subjects for study for this Association!

The normal vital processes depend on two powers, the cells and the blood. The very structure and function of the former are acted upon or built up by the latter. Thus it appears, as our master Virchow has lately pointed out, that finally we return to a species of humoral pathology, but not indeed to the crases and diatheses of old. For modern humoral pathology looks for the presence in the blood of actual agents mostly of chemical nature. Part of them has been shown to be so; in the case of others we have to rely on inference. Still, with peptones, aceton, sugar, with acetic, lactic, oxalic, uric, and oxybutyric acids in the blood we are fairly acquainted; and the discovery of Fraenkel's thyreo-antitoxin proves to what extent the action of the organic juices is mainly, if not altogether, chemical.

The interests of the practitioner and his patients, of medical science and the commonwealth, are equally served by these views when tested by practice. As an Association we have to deal with the interests of science and of the community; of the latter even more than it is willing to understand or admit. We, however, need not be exhorted to continue our work. The misunderstood sympathy with the alleged sufferings of animals, and the agitations of the anti-vivisectionists—no matter

whether merely misinformed or fanatical—must not swerve us from studying, from learning, and from serving mankind by combining our efforts for public purposes. The hygienic interests of the community are, or ought to be, in our keeping. Your Association being the scientific representative of internal medicine in America, ought to be recognized all over the Union as the scientific lawgiver. What the New York Academy of Medicine is calculated to become for New York City, this Association ought to be able to be for the Union and beyond it through the scientific labors of its members. In order, however, to attain this destiny, let us not forget that medicine must be one and inseparable, now and forever.

Some of our colaborers have left us during the past year. Dr. James Edmund Reeves, who was a member since 1887, and died at Chattanooga, Tenn., on January 4th, at the age of sixty-six years, was one of those who happily blended a strictly scientific ambition, as exhibited by his *Practical Treatise on Enteric Fever* and his *Manual of Medical Microscopy for Students, Physicians, and Surgeons*, also by his paper contained in Vol. V. of our TRANSACTIONS, on "Some Points in the Natural History of Enteric or Typhoid Fever," with a sense of duty both as a public servant and a citizen. From his early professional years he interested himself, both as a fellow of scientific societies and as a health officer, in public hygiene. He was the author of the law creating the State Board of Health of West Virginia, and it was he who felt bound and was able to take up, single-handed, a successful fight against a "consumption cure." At a time when the practice of medicine is frequently degenerating into a trade, and the number of quacks, and especially consumption quacks, is swelled even from among the ranks of men armed with medical diplomas and possessed of official positions, his undoubted courage and moral strength are bright examples that should not be forgotten.

What I said of the combination of special medical interests, and the instincts and aims of a good citizen, is also due to the memory of Dr. James West Roosevelt, who died in New York on April 11th. He was, though a member of this Association since 1889, one of the youngest of us, being but thirty-eight years old when he died. More extensive obituaries will refer to his various monographical contributions to medical literature. In Vol. VI. of our *Transactions* there is a paper of his on the "Frequency of the Localization of Phthisis Pulmonalis in the Upper Lobes." As he was versatile, enthusiastic, and unselfish, his participation in the fight against misrule in New York was active indeed. It will always be gratefully remembered. He was deeply interested in

the efforts of the New York Academy of Medicine to abolish the pollution of the Croton water-shed, and to secure national control of quarantine.

As death is busy causing losses, it is our responsibilty to see that the ranks of the Association remain closed. There being, however, but few vacancies in our roll of one hundred, but few candidates will be presented to you for election. You recollect that in last year's meeting you declined to increase our membership, which is now limited to one hundred. The same proposition will be made again, to be voted upon next year. The class of men to join, and capable of doing scientific work, is certainly growing. Now it is true that the Association has been justly conservative, but conservatism is not narrow. As it was the pride of everyone of us to be one of the hundred, it will, when we conclude to facilitate new admissions, be our pride and happiness to know that no increase of membership will ever include all the Americans willing and able to render actual scientific services to universal medicine.

The minutes of the last meeting were accepted as printed.

In accordance with the recommendation of the Council, it was resolved that the Representative of the Association on the Executive Committee of the Congress of American Physicians and Surgeons be instructed to arrange for a conjoint discussion to be participated in by the Association of American Physicians, the American Pædriatic Society, and the American Physiological Society.

On motion of Dr. Sternberg, it was resolved that the Secretary of the Association be requested to receive contributions to the Pasteur Memorial Fund from members of this Association, and to transmit them to the Pasteur Memorial Committee.

The report of the Treasurer was received and referred to an auditing committee consisting of Drs. Musser and Rachford.

Dr. Busey made a statement in regard to impending legislation in Congress prohibiting vivisection, and moved that a committee consisting of five members be appointed to appear before the Senate Committee in opposition to this bill, and to present a memorial to Congress protesting against the passage of the bill. (Senate Bill, S. 1552.) This motion was carried, and the President appointed as members of this committee Drs. Welch, Pepper, Vaughan, Edes, and Theobald Smith.

The following amendment to the Constitution was presented: "We, the undersigned, move that Section II. of the Constitution be amended by adding the words "twenty-five" at the end of its first sentence; so that the first sentence shall read, "The number of active members shall be

limited to one hundred and twenty-five." Signed by A. Jacobi, George B. Shattuck, William Osler, J. H. Musser, and J. E. Graham.

Dr. F. H. Williams then read a paper on the X-rays, and exhibited photographs taken by them and a fluoroscope. This paper was discussed by Drs. Sternberg, Ernst, Osler, and Ward.

Dr. Rachford then read a paper entitled "Leucomaïn-poisoning, Continued," which was discussed by Drs. Vaughan, Osler, Baumgarten, Putnam, Meltzer, Da Costa, and Rachford.

Dr. Vaughan, on behalf of himself and Dr. Perkins, read a paper entitled "A Toxicogenic Germ Found in Ice Cream and its Chemical Products," which was discussed by Drs. Osler, Welch, Meltzer, and Jacobi.

Adjourned at 1.40 P.M.

Afternoon Session.

The Association was called to order by President Jacobi at 2.45 P.M.

Dr. Flexner read a paper entitled "A Statistical and Experimental Study of Terminal Infections," which was discussed by Drs. Sternberg, Bond, T. Smith, Bolton, and Flexner.

Dr. Abbott then read a paper entitled "The Effects of Acute Alcoholism on the Normal Resistance of Rabbits to Various Forms of Infection," which was discussed by Drs. Meltzer and Abbott.

Dr. Ernst then read a paper entitled "The Identity of the Streptococci and a Description of at least One New Variety," which was discussed by Drs. Sternberg, Abbott, Bolton, and Ernst.

Dr. Theobald Smith then read a paper entitled "Conditions Influencing the Appearance of Toxin in Cultures of the Bacillus of Diphtheria," which was discussed by Drs. Ernst and Bolton.

Dr. Bolton then read a paper entitled "Diphtheria Antitoxin Sometimes Found in the Blood of Horses that Have Not Been Injected with Toxin," which was discussed by Drs. Flexner, Theobald Smith, Jacobi, and Bolton.

Dr. Bolton, in behalf of himself and Dr. Pease, then read a paper entitled "Diphtheria Antitoxin obtained by Electrolysis," which was discussed by Drs. Sternberg, Theobald Smith, Vaughan, and Bolton.

Dr. Abbott then read a paper entitled "The Significance of Pathogenic Spirilla in American Surface Waters," which was discussed by Drs. Vaughan, Theobald Smith, Bolton, and Abbott.

Dr. Vaughan, in behalf of himself, Dr. McClintock, and Dr. Perkins, then read a paper entitled "The Treatment of Anthrax in Rabbits by

Intravenous Injections of Nucleinic Acid," which was discussed by Drs. Theobald Smith, Bolton, Meltzer, and Vaughan.

Adjourned at 5.20 P.M.

FRIDAY, MAY 1ST.—MORNING SESSION.

The Association was called to order at 9.45 A.M. by President Jacobi.

Dr. Theobald Smith then read a paper entitled "Two Varieties of Tubercle Bacillus from Mammals," which was discussed by Drs. Vaughan, Pepper, Sternberg, Abbott, and Smith.

Dr. Henry then read a paper entitled "A Case of Parasitic Chyluria with Filaria Sanguinis Hominis Nocturna in the Blood and Urine," which was discussed by Drs. A. H. Smith, Meltzer, and Henry.

Dr. Pepper, on behalf of himself and Dr. Stengel, read a paper entitled "The Diagnosis and Treatment of Dilatation of the Stomach," which was discussed by Drs. Henry, Fussell, Meltzer, Graham, and Jacobi.

Dr. Musser, on behalf of himself and Dr. Sailer, read a paper entitled "A Case of Leucocythæmia," which was discussed by Drs. Welch and Musser.

Dr. Lyman then read Dr. Danforth's paper entitled "Notes on the Treatment of Pernicious and other Forms of Essential Anæmias," which was discussed by Dr. A. H. Smith, Janeway, Henry, Griffith, Fussell, and Hare.

Dr. Mitchell then read a paper entitled "Certain Effects of Bromic-toxication," which was discussed by Drs. Janeway, Hare, Lyman, Thomson, Dana, Sinkler, and Mitchell.

The Auditing Committee reported that they had examined the Treasurer's accounts and found them correct.

Adjourned at 1.30 P.M.

AFTERNOON SESSION.

The Association was called to order by President Jacobi at 2.45 P.M.

Dr. Griffith read a paper entitled "Idiopathic Osteopsathyrosis in Infancy and Childhood," which was discussed by Drs. Lyman, Musser, A. H. Smith, Hare, and Griffith.

Dr. W. H. Thomson then read a paper entitled "Painful Points in Gouty Compared with Rheumatic Arthritis," which was discussed by Drs. Lyman and Thomson.

Dr. Sinkler then read a paper entitled "Habit Chorea," which was discussed by Drs. Osler, Putnam, Mitchell, Hare, Jacobi, and Sinkler.

Dr. Dana then read a paper entitled "On a Method of Curing Tic Douloureux," which was discussed by Drs. Putnam, Janeway, Lyman, Meltzer, and Dana.

Dr. Putnam then read a paper entitled "The Relation of Migraine to Neuralgias of the Fifth Nerve," which was discussed by Drs. Thomson, Fussell, Janeway, Putnam, and Mitchell.

Dr. Biggs then read a paper entitled "Virulence of the Diphtheria Bacilli Occasionally Found in the Throat in Cases Presenting the Clinical Features of Tonsillitis," which was discussed by Drs. Welch, Meltzer, Jacobi, and Biggs.

Dr. A. H. Smith then read a paper entitled "Prognosis in Pneumonia," which was discussed by Drs. Fussell, Meltzer, Thomson, Hare, Welch, and Smith.

Adjourned at 5.55 P.M.

SATURDAY, MAY 2D.—MORNING SESSION.

The Association was called to order by President Jacobi at 9.40 A.M.

Dr. Garland read a paper entitled "A Case of Œsophageal Hemorrhage with Cirrhosis of the Liver," which was discussed by Drs. Graham, Mitchell, Jacobi, and Garland.

Dr. Meltzer then read a paper entitled "On Absorption in the Stomach," which was discussed by Dr. Jacobi.

The Committee appointed to prepare a memorial to Congress protesting against the passage of the pending bill prohibiting vivisection in the District of Columbia, presented the following, which was unanimously adopted.

MEMORIAL OF THE ASSOCIATION OF AMERICAN PHYSICIANS.

The Association of American Physicians, assembled in annual session at Washington, D. C., May 2, 1896, by unanimous vote and by the appended signatures of its officers and members, hereby records its most earnest protest against such legislation as that proposed by the bill entitled "A bill for the further prevention of cruelty to animals in the District of Columbia"—Senate Bill 1552—in so far as this legislation embodies measures intended to control and restrict experimentation upon animals conducted in the Government laboratories, the medical schools, and other institutions of higher learning in the District of Columbia. In making this protest the Association begs to present to the members of Congress the following considerations:

Experimentation upon animals is an absolutely indispensable and the most important method of investigation of the properties of living organisms, and of the influences which modify these properties. The science and the art of medicine are based upon the knowledge of the structure and the functions of living matter, and consequently in large part upon knowledge which has been obtained by experiments upon animals, and which could have been gained in no other way.

The benefits to mankind of the knowledge thus acquired are of inestimable value. To mention only a few of the results obtained within recent years by animal experimentation, attention is called to the discoveries which have revolutionized surgical practice by the introduction of antiseptic methods of treatment, which have rendered infrequent the occurrence of childbed fever, which have made it possible to prevent the development of hydrophobia after the bite of rabid animals, which have furnished an efficacious method of cure of the otherwise incurable disease, myxœdema, and which, by the antitoxin treatment, have greatly lessened the fatality of diphtheria. By these and similar discoveries derived from experiments upon animals, untold thousands of human lives have been rescued which would otherwise surely have perished.

The saving of animal life itself and the consequent commercial profits resulting from knowledge gained by experiments upon animals have been enormous. The benefits derived from experiments upon animals largely go to the improvement of the public health and the prevention of infectious diseases. Their immediate value is often not recognizable by the individual, unless he has informed himself upon subjects which are in large measure of a technical nature and belong to the study of scientific experts.

It would require a volume to set forth adequately the results, beneficial to mankind and to animals, of knowledge derived from experiments on animals. The assertion of many opponents of vivisection, that knowledge obtained from animal experimentation and which could be obtained in no other way has been of little or no benefit to mankind, can be referred only to ignorance or to wilful misrepresentation.

Never was there a time in which experimental medicine gave promise of results so important for the welfare of mankind as those which we may reasonably expect in the near future, and never was there so little justification as at present to hamper in any way the work of those engaged in searching by the experimental method for means of preventing and curing disease.

Obvious as are such beneficial results of animal experimentation as these specified—and many other similar instances might have been cited

by way of illustration—it should be borne in mind that the full significance of the importance and of the results of experimentation upon animals for the biological and the medical sciences can be adequately appreciated only by those who possess special knowledge of these sciences, and that it is only those who are thus informed who can fully realize the injury which would be inflicted upon these sciences and upon medicine by such legislation as that contemplated in this bill. Upon this matter it is the voice of science and of medicine, which is likewise the voice of true philanthropy, which should be heard and which should control legislative action, and not that of those who, however worthy their impulses, however high their social position, however great their knowledge in other departments, do not possess that special knowledge which renders them competent to judge of the merits of this question.

The voice of science and of medicine, so far as it receives authoritative utterance, is overwhelmingly opposed to legislation of any kind which would take in any measure the direction of experimental medicine and physiology out of the hands of those who on account of their special fitness have been chosen by the authorities of our higher institutions of learning and of research to convey instruction and to conduct investigations in these departments. Unnecessary and offensive in the highest degree would it be by any system of official inspection, such as that proposed in this bill and which might readily be used as a system of outrageous espionage, or by legislation of any kind, to attempt to dictate or control how, and by whom, and for what purposes, and under what conditions, and upon what animals in the laboratories and the institutions of the higher learning experiments shall be made. The decision as to these matters should be left wholly to those in charge of these institutions, who are the ones most competent to judge of them.

Those engaged in the Government laboratories, in the medical schools and the universities of this country, in teaching and investigations which require experimentation upon animals, can be safely intrusted with this function. To say the least, they are not less humane than are those who advocate legislation to control and restrict animal experimentation in these institutions. The assertion which has been made by anti-vivisectionists, that experimentation on animals brutalizes those who witness and practice it, is an insult, without shadow of foundation, to a class of scientific workers devoted to the investigation of problems of the highest importance to the welfare of mankind. Their efforts are to secure the desired knowledge by the infliction of the least possible needless pain upon animals used for experimentation, and we do not hesitate to assert that this solicitude to avoid the infliction of unnecessary pain renders

them more susceptible than the average man to actual cruelty to animals.

We have been unable to learn that there has been a single instance in which abuse has been made of the practice of animal experimentation in the Government laboratories, the medical schools or the universities of the District of Columbia. Any legislation which proposes in any way to control, restrict, or interfere with animal experimentation in these institutions is, therefore, unnecessary, as well as offensive to those who are engaged in the scientific investigations conducted therein.

If there be any doubt as to the opposition of the great body of scientific men and of physicians to such legislation as that proposed in this bill, we beg that Congress will not take action favorable to this bill or to any similar one until sufficient time has been given for a full expression of opinion from scientific and medical associations throughout this country, for the matter is one not merely of local interest, but may concern the future progress of the biological and medical sciences, and of preventive and curative medicine throughout this country.

Dr. Putnam exhibited the charts which accompanied Dr. Folsom's paper on Pneumonia.

Dr. Fussell then read a paper entitled "Dispensaries and their Use in Teaching," which was not discussed.

Dr. Prentiss then read an abstract of his paper entitled "Mescal Buttons," and exhibited specimens.

The following papers were read by title:

"Bacteriological Examinations in Acute Endocarditis," by William H. Welch.

"A Case of Tricuspid Stenosis with other Heart Lesions and Cardiac Liver, with Specimens," by George Dock.

"Abscess of the Spinal Cord," by M. A. Starr.

"A Case of Sub-diaphragmatic Abscess; Diagnosis; Operation; Subsequent Death from Pleurisy of the Other Side," by E. G. Cutler.

"The Pathology and Pathogenesis of Acute and Subacute Diffuse Nephritis," by W. B. Councilman.

"Protracted Simple Continued Fever," by J. M. Da Costa.

"Note on Neusser's Granules in the Blood," by William Osler.

"Hepato-pulmonary Abscess," by William Osler.

"Raynaud's Disease and Erythromelalgia," by J. H. Musser.

"Prevalence and Fatality in Pneumonia," by C. F. Folsom.

"A Case of Wandering Phlebitis (Periphlebitis)," by W. P. Northrup.

"Syphilitic Nephritis," by H. A. Lafleur.

"A Case of Actinomycosis, with Specimens," by T. S. Latimer.

Dr. Isaac Adler, of New York, Dr. John J. Abel, of Baltimore, Dr. D. D. Stewart, of Philadelphia, and Dr. Walter Reed, of U. S. Army, whose nominations were favorably recommended by the Council, were elected members of the Association.

The following gentlemen, nominated by the Councillors, were elected officers for the ensuing year:

President.—J. M. Da Costa.

Vice-President.—Frederick C. Shattuck.

Recorder.—I. Minis Hays.

Secretary.—Henry Hun.

Treasurer.—W. W. Johnston.

Councillor.—I. E. Atkinson.

The thanks of the Association were unanimously voted to President Jacobi for his labors in bringing about such a very successful meeting.

The thanks of the Association were voted to Mr. T. E. Roessle, proprietor of the Arlington Hotel, for his courtesy in furnishing such a commodious room to the Association for its meeting.

Adjourned at 11.45 A.M.

HENRY HUN, *Secretary.*

LEUKOMAÏN-POISONING.

(CONTINUED.)

By B. K. RACHFORD, M.D.,
PROFESSOR OF PHYSIOLOGY AND CLINICIAN TO CHILDREN'S CLINIC, MEDICAL COLLEGE OF OHIO, CINCINNATI, OHIO.

THIS communication is offered as a sequel to the paper on the same subject which I read before this Association last year. At that time I presented the experimental and clinical evidence upon which I based the opinion that leukomaïn-poisoning is a most important phase of autointoxication which may manifest itself in at least three distinct but closely allied clinical types, viz. :

1. Leukomaïn headache (true migraine).
2. Leukomaïn epilepsy (migrainous epilepsy).
3. Leukomaïn gastric neurosis.

Another year of work in this field has enabled me to separate out another clinical type of leukomaïn-poisoning, which I shall call in conformity with the above nomenclature :

4. Leukomaïn asthma.

This form of asthma presents very much the same clinical picture as ordinary bronchial asthma. The attacks, as a rule, come on during the early morning hours, and vary in severity from a simple to the most intense dyspnœa. My impression is that this type of asthma is not uncommon, and that it goes to make up a not inconsiderable proportion of the asthmatic attacks which are classified under the comprehensive term " Bronchial Asthma." However this may be, I am quite sure that the urine passed during certain of these asthmatic attacks contains a very great excess of paraxanthin and other leukomaïns of the uric-acid group, and that the paraxanthin solution separated from the urine of these cases will, when injected into mice, produce intense dyspnœa with the other symptoms of para-

xanthin-poisoning. The following case is offered as an example of leukomaïn asthma:

CASE.—A woman, aged sixty years, of gouty inheritance and strong neurotic tendency; a number of her family have suffered from "rheumatic gout," migraine, and asthma. She and a number of her family have an uncomfortable amount of adipose tissue. For three or four years this patient suffered at times from vertigo and shortness of breath, without apparent cause. These symptoms could not with any certainty be traced to bodily exertion, nervous excitement, indigestion, or any other exciting cause. On February 22, 1895, one of these attacks of dyspnœa culminated in a very severe attack of asthma, which continued in paroxysms for five days. During this time a paroxysm of intense dyspnœa would occur, as a rule, between 5 and 8 A.M. This paroxysm was at times alarming in its intensity, and would continue from one to three hours, but during the attack the heart's action was strong, and the pulse did not reach one hundred. The dyspnœa would diminish after a fit of coughing, with the discharge of considerable quantities of bronchial mucus. The breathing would then get easier, but would remain somewhat embarrassed throughout the entire day, to be again exaggerated into a severe paroxysm the next morning. After the fifth day the patient had no paroxysms of dyspnœa, and very soon thereafter commenced to be convalescent.

During March, April, and May this patient had a number of asthmatic attacks of much less severity than the one described. Since that time (now almost a year) she has not had a single attack of dyspnœa. I was very careful to assure myself that there was no heart or kidney lesion to account for the dyspnœa of this patient.

The urine of this patient, passed during a severe asthmatic attack, was acid, specific gravity 1024, no albumin, no casts, contained an excess of uric acid and a large excess of paraxanthin and xanthin. From one and one-half quarts of urine I separated both xanthin and paraxanthin. The paraxanthin solution separated from this urine was poisonous to mice, the mice dying with the characteristic symptoms of paraxanthin-poisoning, one of which is severe *dyspnœa*. One and one-half quarts of urine passed by this patient in the interval between the attacks did not contain an appreciable quantity of paraxanthin.

Upon this evidence I conclude that paraxanthin was an important factor in producing the paroxysms of dyspnœa from which this patient suffered. In this case, as in others that I have examined, I believe the symptoms were due to an overproduction rather than to a deficient elimination of paraxanthin. I emphasize this point since it will appear later in this paper that I have reason to believe that the dyspnœa (a uræmic symptom) of acute and chronic Bright's disease is in part

due to the deficient elimination of the same leukomaïn, which in very small quantities is one of the ingredients of normal urine.

In this connection I wish also to express the opinion that the characteristic symptom in each of the four types of leukomaïn-poisoning which I have described is produced by paraxanthin, rather than by the less soluble and less poisonous leukomaïns associated with it in these diseases. That is to say, such symptoms as may be produced by xanthin and heteroxanthin are for the most part obscured by the paraxanthin-poisoning. The characteristic headaches, the epileptoid convulsion, the gastralgia, and the asthma may, therefore, very properly be called symptoms of paraxanthin-poisoning.

From this phase of my subject I wish to pass to the study of the group of nervous symptoms so commonly associated with chronic alcoholism and chronic lead-poisoning, since it is my belief that certain of the nervous symptoms which occur in these conditions are in part due to leukomaïn-poisoning.

CHRONIC ALCOHOLISM. The importance of chronic alcoholism as a factor in the production of the gouty diathesis suggested to me the possibility that leukomaïn-poisoning might be a factor in the production of the convulsive seizures which occur in chronic alcoholism, and also of the nervous symptoms which are grouped under the term "delirium tremens." Possessed with this idea, I attempted its solution by an examination of the urine of such patients. Some difficulty was experienced in obtaining suitable specimens of urine, as it had to be collected by catheterization, an operation which is at times attended with difficulty in these obstreperous and delirious patients. I did, however, succeed in getting three fairly representative specimens of delirium-tremens urine, and from the examinations of these urines I concluded that paraxanthin was a factor in producing the nervous symptoms from which chronic alcoholics so commonly suffer.

One of these cases, which occurred at the Cincinnati Hospital in the service of Dr. George Fackler, is here given in detail. The urine was kindly collected by Dr. Shield, the resident physician:

CASE NO. 72,461.—J. K., aged thirty years, teamster, an American, single, male, and of fair physique, was admitted to the Cincinnati Hospital, November 18, 1895. Family history of phthisis, otherwise negative. Personal history: He has hemorrhoids, denies venereal disease, but admits chronic

alcoholism extending over a period of two years. He never had delirium tremens before, but recently he has been very nervous except when under the influence of liquor. He drank whiskey before breakfast to "settle his stomach and quiet his nerves." After a week of very hard drinking he was brought into the hospital suffering from delirium tremens; was so unruly that it was necessary to strap him to the bed. In his delirium he was selling potatoes. The physical examination, apart from the tremor, revealed nothing of importance; the urine was saved by catheterization. Patient was ordered bromide of potash, grs. xxx, and hydrate of chloral, grs. xx, every three hours, when awake.

November 19*th*. Slept some; is delirious when awake.

20*th*. Slept all night; still delirious.

21*st*. Slept well; no delirium.

25*th*. Discharged well.

Examination of two quarts of urine excreted on November 18th and 19th: Specific gravity 1020, acid, yellow, no albumin. An excess of uric acid and a small quantity of paraxanthin were found. The final fluid was evaporated to two cubic centimetres, and this fluid in large doses produced paraxanthin-poisoning when injected into mice.

From a study of this and two other cases I concluded that paraxanthin is present in excess in the urine passed by patients suffering from delirium tremens. In the light, therefore, of the known poisonous properties of paraxanthin, the inference seems fair that this leukomaïn is one of the factors which assist in producing the nervous symptoms of delirium tremens and the convulsive seizures of chronic alcoholics.

LEAD-POISONING. The fact that chronic lead-poisoning may be the all-important factor in the production of the gouty diathesis suggested the possibility that leukomaïn-poisoning might be a factor in the production of lead encephalopathy, and possibly other of the nervous symptoms of chronic lead-poisoning. It is an interesting fact that the groups of nervous symptoms which may result from chronic lead-poisoning and chronic alcoholism are very similar to the group of nervous symptoms which may occur in the gouty diathesis. The migraine, the epilepsy, the gastric neurosis, and the asthma, which are among the classical symptoms of so-called masked gout, and which I have demonstrated to be due to leukomaïn-poisoning, have their analogues in the paroxysmal headaches, the epileptoid convulsions, the gastro-intestinal attacks, and the dyspnœa, which not infrequently occur as symptoms of chronic lead-poisoning and chronic alcoholism.

J. C. Wilson, in his paper[1] on "Chronic Lead-poisoning," says:

[1] Pepper: System of Medicine, 1886.

"Naunyn has pointed out the resemblance between the nervous and psychical derangements in lead encephalopathy and those which characterize chronic alcoholism, and suggests that lead, like alcohol, produces these effects, not as a direct poison, but indirectly, in consequence of abnormal nutrition of the whole system brought about by the continued circulation of a foreign poisonous material in the blood."

It will presently be seen, in the light of my investigations, how strangely near the truth is this fortuitous suggestion of Naunyn, since my studies during the past year, the result of which I here present, have convinced me that the epileptoid convulsions, one of the most characteristic symptoms of lead encephalopathy, are due to the direct action on the nervous centres of paraxanthin, which exists in enormous excess in the urine of these cases. Only one case of well-marked lead encephalopathy occurred in the Cincinnati Hospital during the past year, and that case is here reported by the courtesy of Dr. Joseph Eichberg, in whose service it occurred.

CASE I.—A. S., German, aged fifty-five years, of good physique, has been a lead-worker for years, but has never had an attack of lead-poisoning before.

September 29, 1895. He was brought to the hospital in a semi-comatose condition which had followed an epileptiform convulsion. It was learned that he had been sick only two days, and had never had a convulsion prior to this one, which caused him to be sent to the hospital. For some hours after entering the hospital he was slow to understand and answered questions in an incoherent way. His bowels were constipated and his stomach irritable. Temp. 97°, pulse 68, resp. 20. Physical examination: Patient has a blue-line in the gums, a coarse tremor of the hands, and a weakness of the extensor muscles of the forearms; tongue is coated, but moist, and shows marks of fresh laceration, evidently caused by the teeth in the convulsions previously mentioned. His abdomen is retracted, but he complains of no pain or tenderness in it. His heart, lungs, and spleen are normal.

Treatment. Epsom salt ʒj every hour till bowels have moved freely.

October 1. Slept well, temperature and pulse normal, mind has remained sluggish, bowels have been kept open with salts.

2*d*. At 6 P.M. he had an epileptoid convulsion; the muscular spasm was in the beginning clonic and afterward tonic.[1] He frothed at the mouth and lacerated his tongue during this convulsion, which lasted three minutes. Violent delirium immediately followed the convulsion and continued till 8 P.M. He was given $\frac{1}{150}$th grain of hyosin, and thirty grains of bromide of potash.

[1] I have arranged but not otherwise changed these notes which were taken by resident physician Dr. Robert Jones, who materially assisted me in obtaining the specimens of urine from his patient.

At 2 A.M. he went to sleep, and slept till morning. The nurse was ordered to save the urine passed immediately following the convulsion. One quart in all was procured for examination.

3*d*. He is rational and calm this morning after his sleep, and answers questions fairly well. His bowels are constipated. His breath is foul, and there is slight tremor. He was given Epsom salt.

6*th*. Has been doing well; sleeps all night and complains of nothing except slight pain in bowels, probably from the salts, which have been given every day to keep bowels open. Urinalysis: Urine yellow, sp. gr. 1020; acid; no albumin; no sugar; but lead reaction was well marked. (Previous to this time the urine had not been examined for lead.)

8*th*. Patient feels well, sleeps good, has a fair appetite, there is a slight tremor present, and extensors of left hand are still weak.

10*th*. Patient doing well; ordered comp. tinct. of cinchona ʒj and tinct. nux vomica gtts. v three times a day.

20*th*. Has not complained of anything during the past ten days; his bowels have been kept open, his appetite has been good, and he seems securely convalescent. During the past two days two and one-half quarts of his urine were saved for examination, for the purpose of comparison with the urine passed just after the convulsion.

Examination of Urine. Specimen No. 1. One quart of urine, passed after the convulsion of Oct. 2d, contained lead and a large increase of uric acid; sp. gr. was 1024. It contained no albumin and no sugar, but the special purpose for which the urine was saved was to determine the presence or absence in it of *xanthin* and *paraxanthin*. This urine was therefore examined for these bodies by the methods set forth in my paper on "Leukomaïn-poisoning,"[1] and found to contain a trace of xanthin and a *considerable quantity of paraxanthin*. The great increase in the quantity of paraxanthin present in this urine can best be appreciated by remembering that nine litres of normal urine are necessary to demonstrate its presence (Salomon), while in this specimen, from one quart of pathological urine, paraxanthin was found in considerable quantities.[2]

[1] TRANSACTIONS OF ASSOCIATION OF AMERICAN PHYSICIANS, 1895, vol. x., and New York Medical Record, June 22, 1895.

[2] The chemical tests which I use for determining the presence of xanthin and paraxanthin in the "final fluid" are as follows:

Xanthin I. A drop or two of the suspected liquid and two drops of C. P. nitric acid are evaporated over an alcohol lamp. When xanthin is present a lemon-yellow residue is left. This is not changed by ammon. hydrate, but changes into a purple-red with potassium hydrate.

II. A few drops of the suspected liquid are mixed with very little bleaching-powder and sodium hydrate in a water glass. The solution becomes covered by a dark-green scum which changes into brown and then disappears.

Paraxanthin I. A few drops of a concentrated solution of potassium or sodium hydrate are added to a few drops of the suspected liquid; a white, glittering precipitate is formed if the suspected solution contained very much paraxanthin; if little paraxanthin is present, the solution will be only cloudy, but will increase in cloudiness after standing awhile.

II. A few drops of the suspected liquid are mixed with a little chlorine water containing a trace of nitric acid and evaporated; when dry they are exposed to an ammoniacal atmosphere, if paraxanthin is present a beautiful rose-red color is produced.

Following the chemical tests I subjected the "final fluid" to the physiologic test for paraxanthin, by injecting it into mice. In a very large number of examinations I have never failed to produce paraxanthin-poisoning in the mouse, when the chemical examination showed that paraxanthin was present, and I have always failed to produce paraxanthin-poisoning in the mouse with a "final fluid" in which the chemical examination said that there was no paraxanthin. For a detailed account of the symptoms of paraxanthin-poisoning in the rat and mouse the reader is referred to a previous publication.[1] It will be sufficient here to say that the convulsion is one of the most striking and characteristic symptoms, and that in the beginning the convulsion is clonic and afterward becomes tonic or tetanic. It should here be noted, by reference to the note in the above history made by the resident physician on October 2d, that the "epileptiform convulsion" which this patient had on that date resembled a paraxanthin convulsion in the mouse; that is to say, it was "in the beginning clonic and afterward tonic." In the light of these facts the physiologic test of the "final fluid" from the urine of this patient assumes special importance. This test was made in the presence of Dr. F. Southgate and Mr. H. Wherry, who assisted me in making these observations. Three minims of the "final fluid," when injected into the back of a mouse, produced death in five minutes. The mouse died in convulsions, and the muscular movements were at first clonic and then tonic or tetanic.

There is yet one other important bit of evidence which must come in before one can pass judgment on the cause of the convulsion which this patient had on October 2d, and that is, that in the specimen of urine (two and one-half quarts) passed by this patient during his convalescence, on October 19th and 20th, I failed to detect paraxanthin, and only a trace of xanthin was found. In my former papers I have noted the fact that an excess of paraxanthin in the urine means that, previous to its excretion, there was an excess of paraxanthin in the blood.

In view of all the facts above given it seems a rational conclusion that the convulsion which this patient had on October 2d was due to an excess of paraxanthin in his blood; this paraxanthin was excreted and found in excess in the urine passed immediately after the convulsion, and when separated from the urine produced the same kind of a convulsion in the mouse.

CASE II.—D. C., aged thirty-five years, has been a lead-worker for years and has had lead colic twice before.

June 1, 1895. He was admitted to the Cincinnati Hospital suffering from

[1] Medical News, May 26, 1894.

lead-poisoning. The blue-line on margin of gums was well marked. Patient had a severe attack of lead colic which lasted twelve hours. Two quarts of urine, passed during and subsequent to the attack, were saved and examined for xanthin and paraxanthin.

5th. Man discharged well; he had only the one paroxysm of pain, and was convalescent the next day.

Examination of Urine. Two quarts passed during and after an attack of lead colic contained *no paraxanthin*, but contained *considerable xanthin*. The "final fluid" when injected into mice did not produce convulsions.

CASE III.—F. M., aged forty-one years, lead-worker, was admitted to Cincinnati Hospital September 18th, and discharged September 21, 1895. During the three days he was in the hospital he suffered from lead colic, and was discharged "improved" at his own request. The attack of colic was not very severe, and was accompanied by arthralgia.

Examination of Urine. Two quarts of urine failed to show the presence of paraxanthin, but xanthin was present in excess. The "final fluid" in small doses was not poisonous to mice.

In these urine examinations it will be noted that the patient who had "considerable" paraxanthin had little xanthin in his urine, and that the patients who had "considerable" xanthin had no paraxanthin in their urine. The same observation was made in the examination of a number of urines of different kinds; very commonly when xanthin was found in excess no paraxanthin was found, and it was also observed that the presence of xanthin or paraxanthin in excess did not necessarily indicate an excess of xanthin. I may also remark in this connection that the presence of xanthin or paraxanthin in excess in the urine was not always associated with an excess of uric acid in the same urine.

REMARKS ON THE PATHOLOGY OF LEAD-POISONING. From the evidence given in this and in my previous paper, the conclusion I think is justified that xanthin and paraxanthin play an important *rôle* in the production of those nervous symptoms of chronic lead-poisoning which cannot be explained by degenerative changes in nerve-tissue. Included in this group of functional symptoms may be mentioned amblyopia, headache, vertigo, neuralgia, colic, arthralgia, delirium, convulsions, and temporary insanity. This group of nervous symptoms has never been satisfactorily explained by the pathological findings in chronic lead-poisoning. Neither has any theory of this disease been comprehensive enough to furnish a rational explanation of these symptoms. One cannot understand how the direct

action of lead on the nervous system can produce this group of symptoms, but one can understand how, in the perverted metabolism going on in degenerating muscles, nerves, and other tissues, not only uric acid, but also the closely allied uric-acid leukomaïns, xanthin, paraxanthin, and heteroxanthin may be formed in such excess as to make them potent factors in the production of the above-named nervous symptoms. This theory, founded, I think, for the most part on fact, does not detract from the important *rôle* which the direct action of lead on tissues plays in the pathology of this disease. To the action of lead may be attributed the impaired nutrition and the degenerative changes in nerve- and muscle-tissue. In short, lead may be accused of producing all the morphological changes which are recognized as a part of the pathology of chronic lead-poisoning, leaving to xanthin, paraxanthin, heteroxanthin, and possibly other poisons of this class the production of the above-named nervous symptoms, which cannot be explained by structural changes.

In this connection it is impossible for me to resist the temptation of calling attention to the remarkable similarity which exists between the nervous symptoms of gout and the nervous symptoms of chronic lead-poisoning, and of further noting the fact that these two conditions have almost the same pathological anatomy. This may be taken as evidence that the one pathological factor—leukomaïn-poisoning—which, as I have demonstrated, these two morbid conditions have in common, may possibly have something to do with the structural changes as well as with the nervous symptoms which occur in these two diseases. Concerning this question I shall have something to say in a later communication. I pass it for the present, that I may call your attention to another most important phase of autointoxication, viz.:

Uræmia. In this, the closing paragraph of my paper, I shall not have time to discuss the broad subject of uræmia. It is my purpose, therefore, here merely to present a portion of the evidence which has convinced me that paraxanthin is a very important factor in producing the symptom-complex which we call uræmia. In considering this subject I would ask that the following statements be kept in mind:

1. Paraxanthin-poisoning in the mouse is characterized by an increased reflex excitability, which is followed by stupor, dyspnœa, and

convulsions. The convulsions are in the beginning clonic and then become tonic or tetanic.

2. In this and previous communications I have demonstrated that paraxanthin may be an important factor in producing the following symptoms, viz.: headache, gastric pain and gastric irritation, asthma, and convulsions.

3. The most characteristic symptoms of uræmia are headache, gastric irritation, dyspnœa, stupor, muscular twitchings, and convulsions.

The above statements are here presented, since their suggestiveness led me to inquire into the presence or absence of paraxanthin in the blood of uræmic cases:

CASE No. 66,104, aged fifty-seven years, peddler, American, single, of good physique, was admitted to Cincinnati Hospital January 11, 1896, for soft chancre. He had syphilis nine years ago. At time of his admission to hospital he had diarrhœa, a paroxysmal cough, œdema of feet, and a sore about the size of dime on the under surface of prepuce. His urine contained albumin and casts. He remained in the surgical ward till February 21st, when he was transferred to the medical ward (service of Dr. J. C. Culbertson) because of well-marked uræmic symptoms which had recently developed. At this time the œdema was marked, the cough was paroxysmal, he was delirious, passed his urine involuntarily. His wild delirium gradually gave way to stupor which on February 24th deepened into a semicomatose condition. At this time 200 c.c. of blood were removed from the patient's right arm, but no improvement followed this venesection. The uræmic symptoms deepened and he died in uræmic coma on February 25th.

Post-mortem examination confirmed the diagnosis of death from uræmia due to interstitial nephritis.

Examination of the 100 c.c. of blood which were obtained by venesection on February 24th, when the patient was in semicomatose condition, revealed the presence of paraxanthin, but not a trace of the other xanthin bodies. The paraxanthin solution obtained from the blood of this patient killed mice with the characteristic symptoms of paraxanthin-poisoning.

I cannot be mistaken in the fact that paraxanthin was obtained from this blood. But there are other sources of error which must be investigated before paraxanthin can be justly accused of taking part in the production of the symptoms from which this patient suffered. In the first place, we must inquire whether paraxanthin can be found in normal blood when subjected to the same method by which paraxanthin is found in uræmic blood.

To answer this question I examined 250 c.c. of my own blood which I obtained by venesection from my arm. In this blood I failed to find even a trace of the xanthin bodies. And I therefore concluded that paraxanthin did not exist in appreciable quantities in normal blood, and that it was not developed in blood while being subjected to the process by which the xanthin bodies are isolated.

The second question to be inquired into, as a possible source of error, is, Cannot paraxanthin be found in the blood of a patient dying from any disease? Or, in other words, is it not possible that the paraxanthin may result from some abnormal body-chemistry which shortly precedes death?

In answer to this question I examined the blood of a Cincinnati Hospital patient, No. 73,746, from the service of Dr. J. C. Mackenzie. This patient was admitted to the hospital on March 8, 1896, in a comatose condition. On March 10th he was bled from the median veins in both arms. About 400 c.c. of blood in all were taken. The patient died the next day, March 11th, and the post-mortem examination revealed the fact that he died from cerebral hemorrhage. In the 400 c.c. of blood obtained from this patient I failed to find paraxanthin. The type of unconsciousness in this case was very like that which occurred in the case of uræmia above reported, but in one instance the coma was produced by uræmia and in the other by cerebral hemorrhage.

In the light of these facts, therefore, I am of the opinion that paraxanthin is an important factor in producing that complex of symptoms which we call uræmia.

DISCUSSION.

DR. V. C. VAUGHAN: This communication by Dr. Rachford is exceedingly interesting and valuable. I would like to ask what method he used in the separation and identification of the xanthin bases, and also as to whether there was any leucocytosis in these cases. The present trend of opinion is that the xanthin bases come from the nucleated cells—the nuclei of the cells—and it would be interesting to know whether or not he has made any count of the white blood-corpuscles in these cases.

DR. OSLER: I think the Association is to be congratulated that one of its members at least is paying some attention to this extremely interesting sub-

ject, which, as many of you know, is being worked at industriously in certain of the clinics in Europe, particularly in Professor Neusser's. I would like to ask Dr. Rachford whether he has studied the presence of Neusser's granules in these cases. I had intended to make a short communication on the subject of the presence of these bodies, but the material which I have on hand is scarcely sufficient. Neusser noticed that with a slight modification of Ehrlich's methods in all instances of the so-called uric acid diathesis there were seen, surrounding the nuclei of the leucocytes, certain dark, granular bodies which he regarded as pathognomonic of the uric acid diathesis and of gout; and he thought that possibly they were related to the xanthin bodies. It is certainly remarkable in what extraordinary numbers these dark granules occur in a majority of cases of gout. It would be very interesting to know if in these cases of xanthin-poisoning these granules were present in large numbers in the leucocytes. The subject is one of greatest interest. The studies which have come from Neusser's laboratory indicate the possibility of the existence of a xanthin diathesis closely related to the gouty condition.

DR. J. J. PUTNAM: I would like to ask whether Dr. Rachford has studied the urine in the intermediate stages of epilepsy, as to whether paraxanthin occurs in increasing amounts, culminating with the attack. I would also like to know whether paraxanthin is to be found in the urine after epileptic attacks brought on experimentally, as by irritation of the cerebral cortex.

DR. MELTZER: I would like to ask whether the paraxanthin bodies have been found in the urine after convulsions from other sources, for instance, strychnine-poisoning.

DR. DA COSTA: One or two points have occurred to me in connection with this valuable paper which it seems might be well to bring before the Association. If these observations should be fully confirmed in the future, it would do away with a great difficulty in explaining why it is that two processes apparently so entirely dissimilar as chronic lead-poisoning and gout should both lead to contracted kidney. If these observations, which are so ingenious and suggestive, stand, and if it be established that these leukomaïns and derivatives be present in both these dissimilar states, it is easy to understand that one common cause would lead to the same organic changes in the kidney in each condition.

DR. RACHFORD: In answer to Dr. Vaughan's question, I would say that I depended for the identification of these bodies chiefly upon the physiological test. The chemical test which I used for determining the presence of xanthin and paraxanthin in the final fluid were those given in the little book of which Dr. Vaughan is the author. In the appendix to the paper which I read before this Association last year I published the method used for the isolation of the xanthin bodies. When the chemical test indicated that paraxanthin was present I was always able to produce characteristic paraxanthin-poisoning in the mouse, which is, first a stupor followed by slight

muscular twitching, then the muscular twitching passing into tonic or tetanic convulsions. During the whole of this period the mouse has marked dyspnœa.

In a number of these cases of headache in which I made an examination of the blood I did not find any leucocytosis. I have not examined for Neusser's granules. Uric acid and urea were found in the blood of the patient who died from uraemia.

As I have reported in previous papers, I have examined these patients in the intermediate stages, and have always failed to find paraxanthin present until the symptoms of paraxanthin-poisoning appear, the headache, the epilepsy, the gastric neurosis, and the asthma. In all of these cases I have examined the urine repeatedly in the interval, and have always failed to find paraxanthin present. In a certain class of cases in which there are joint-symptoms and symptoms of arterial sclerosis I have been able to detect the other xanthin bodies sometime before an attack. In a case of arterio-sclerosis with gouty attacks, which I have been studying for some time, I find that the patient excretes the xanthin bodies in excess during these attacks, and that immediately following these attacks the urine is entirely free from them. Then very shortly the xanthin increases in quantity until it culminates in one of these attacks.

I would insist upon calling attention to the fact that leukomaïn epilepsy differs from the ordinary type of epilepsy. I have repeatedly examined the cases of ordinary epilepsy, and have always failed to find paraxanthin in the urine. This form of epilepsy, which I have designated as leukomaïn epilepsy, comes on, as a rule, in middle life, and usually follows a sick headache of former years. At one time the patient may have leukomaïn epilepsy, at another time a severe leukomaïn headache. These cases constitute a distinct type of epilepsy.

A POISON-PRODUCING BACILLUS FOUND IN ICE-CREAM AND CHEESE.

By VICTOR C. VAUGHAN, M.D.,

AND

GEORGE D. PERKINS, Med. Student,

OF ANN ARBOR, MICHIGAN.

History. In August, 1895, we received a glass jar containing a small quantity of ice-cream which had poisoned a number of people at a small village in Northern Michigan. In October of the same year Dr. Morris, of Vassar, Michigan, sent to us a small portion of cheese which had caused alarming illness in a number of people of that place. These samples of suspected food were examined by the method which we employ in such cases at the Laboratory of Hygiene of the University of Michigan, and which we have published elsewhere. The poison-producing germ was found to be the same in the two articles of food, a fact which was suggested by the similarity in the symptoms observed and reported by the attending physicians at the two places.

Symptoms. Some fifty people partook of the cream, and all were more or less seriously affected. The number known to have suffered after eating the cheese was twelve. There were no deaths. The symptoms appeared from three to six hours after the food was eaten. The first evidence of illness consisted of nausea, which in all instances was followed by vomiting. Diarrhœa was present in the majority, but not in all. The vomiting was accompanied by sharp pains through the abdomen, and it is stated that in some the pain was partially relieved by strong pressure. The most alarming phenomenon observed by the physicians in attendance was feebleness of the heart's action. The hands and feet grew cold, then the entire body became cool and clammy, and in many the radial pulse was not perceptible. This con-

dition, together with a heavy stupor in some, gave occasion for alarm to the attending physicians, and hypodermic injections of brandy, digitalis, strychnin and nitroglycerin were employed, each physician selecting the stimulant in which he had most confidence, or taking that which he had at hand. In some, the pupils were said to be dilated, but the evidence on this point is confined to the testimony of one physician. In one instance the patient became wildly delirious, crying out, and attempting to rise from bed. Those who vomited but little and had no diarrhœa fell into a heavy stupor, and it is highly probable that these were in greater jeopardy than any of the others. The early and thorough vomiting doubtlessly was the most potent agent in saving those who had taken the larger quantities of the infected food. As has been stated, the depressing action of the poison on the heart impressed the physicians in attendance so markedly that all mention it, and one who had seen other cases of cheese-poisoning thought that the active agent in this instance must differ from that which had caused the sickness previously observed by him.

Morphology of the Germ. The infecting organism in the ice-cream and cheese is a bacillus, which grows readily both in aërobic and anaërobic cultures. The form of the bacillus is subject to some variations, dependent upon the medium on which and the conditions under which it is grown. Usually it forms rods the length of which is from two to three times its breadth. Under most conditions the rods are single, but at times an end-to-end growth of from two to four bacilli may be seen. Threads are sometimes formed, and in other instances the coccus-form may be approached, but never reached. Germs taken from an agar-tube, after twenty-four hours' growth in the incubator, gave an average length of 1.72μ and a breadth of 0.86μ. The formation of spores has not been observed.

Behavior with staining reagents. Germs taken from agar-tubes after eight days' growth in the incubator fail to stain with methylene-blue, even after being heated or after being left in the stain at ordinary temperature for five minutes, but do stain readily with carbolic fuchsin. Preparations made from the tissues and fluids of the bodies of animals dead from the effects of the germs take all the basic anilin dyes readily. By Gram's method the bacillus is decolorized. In staining tissue containing the germ the best results are obtained with Löffler's methylene-blue and a contrast with eosin.

Motility. From tubes grown in the incubator this bacillus shows marked motility, which is, however, much less noticeable in cultures grown at ordinary temperature.

Growth on gelatin. Stab-cultures in gelatin show a continuous growth along the needle track, and spread slightly about the point of inoculation on the surface. There is no liquefaction, and after twenty-four hours or longer one or more gas-bubbles may be seen along the line of growth. The surface growth is white, while that along the line as seen through the gelatin is yellowish. "Shake" tubes in gelatin begin to grow cloudy after from sixteen to twenty-four hours, and later numerous small gas-bubbles form. These bubbles grow larger for a few days and then gradually disappear. On gelatin plates the colonies show considerable variety of form; many are round, others are oval, and some quite irregular in outline. The superficial colonies appear granular and spread about a more dense nucleus. Blue litmus gelatin soon becomes red and cloudy; later, the color wholly disappears.

Growth on agar. On ordinary agar in inclined tubes the growth spreads over the surface, and has a white, slightly glazed appearance. Stab-cultures grow well along the line and spread over the surface. Glucose agar cultures show abundant white growths, spreading over the surface and producing gas in the deeper layers. Glycerin agar-tubes are similar to those of glucose agar, with the exception of the fact that no gas develops in the former.

Growth in beef-tea. Beef-tea cultures grown at 37° become cloudy after about twelve hours, and later a pellicle forms, and through this gas-bubbles may be seen arising. After from three to four days the bacterial growth subsides, leaving the supernatant fluid quite clear. Glucose beef-tea-tubes evolve larger quantities of gas.

Growth in milk. Milk is coagulated by this bacillus within from twelve to fourteen hours, when kept at 37°. Later coagulation becomes complete, and the fluid separates into a coagulum and a whey. Milk cultures soon develop a pleasant odor of butyric ether, and this persists so long as the culture remains uncontaminated. The development of acid is accompanied by the liberation of gas. This continues until all the milk sugar is consumed, and for this a period of about one month in litre flasks is required. Milk rendered feebly red with rosolic acid is decolorized after two or three days in the incubator.

This bacillus decomposes glucose, lactose, sucrose, maltose, dextrin, starch, and glycogen.

On blood-serum. On this medium our bacillus forms a thin white or yellowish growth.

On potato. Our bacillus forms a yellowish, thick, slimy, raised growth and develops a sour odor. This growth is the same whether the surface of the potato be naturally acid or alkaline, or be rendered feebly alkaline with sodium carbonate.

Growth on other vegetables and fruits. This bacillus grows well on turnip, beet, sweet potato, onion, parsnip, carrot, banana, and apple. The growth on turnip is abundant, grayish, and moist; on beet, white and glazed; on sweet potato, dry and white; on onion, white and slimy; on parsnip, yellowish, and evolving much gas; on carrot, an abundant, raised creamy growth, of sour odor; on banana, slightly elevated and slimy; on apple, thin and white. Cultures of this bacillus on these fruits and vegetables were made on account of the well-known observation that milk kept near decomposing fruits and vegetables frequently causes unpleasant symptoms in those drinking it.

Growth in Uschinsky's fluid. A culture medium free from proteid material was employed. The following, which is one of Uschinsky's formulæ, was selected:

Glycerin	40 parts.
Sodium chloride	7 "
Calcium chloride	0.1 part.
Magnesium sulphate	0.4 "
Dipotassium hydric phosphate	2.5 parts.
Ammonium lactate	6 "
Sodium asparginate	3.4 "
Water	1000 "

In this fluid our bacillus grows abundantly, and these cultures were utilized, as will be seen later, in the study of the chemical poisons produced by the bacillus. One interesting fact was observed in this connection, and, if properly interpreted by us, it shows that the presence of potassium in the culture medium is a necessity for the growth of this bacillus. When disodic hydric phosphate was substituted for the corresponding potassium salt in the above formula, the germ failed to grow and the fluid became sterile. This was tried in six flasks, and there was absolutely no growth in any of them. The only alteration

in the fluid was the substitution of the sodium for the potassium salt.

Effects of temperature on growth. This germ finds its optimum temperature at about 38°. However, it develops well at any point between this and 25°. Below the last-mentioned temperature growth is slow, or fails altogether. Beef-tea cultures were kept frozen for twenty-nine days without destroying the vitality of the bacillus. Alternate freezing and thawing carried through the same time likewise failed to kill.

Twenty beef-tea-tubes were inoculated with this germ, and kept in an air-bath at from 40° to 45°, and one tube was removed at the expiration of each hour and placed in the incubator at 37°. All of these tubes developed, thus showing that an exposure of twenty hours at this temperature does not kill. A temperature of from 45° to 50° maintained for thirty-one hours failed to kill, while the same temperature for forty-seven hours did kill. Another experiment showed that exposure to the last-mentioned temperature for thirty-five hours did destroy the germ.

A beef-tea culture which had been growing for twenty-four hours in the incubator at 37° was placed in an air-bath, kept at 54°. A loop of this culture was removed at the expiration of each hour, and a gelatin plate made from it. The number of germs on each plate was counted after twenty-four hours, with the following results: One-hour plate, 207 colonies; two-hour, 156; three-hour, 91; fourth-hour, 54; fifth-hour, 25; sixth-hour, 3; seventh-hour, 3; eighth-, ninth-, and tenth-hour, no growth.

Thirty beef-tea-tubes were inoculated and placed in a steam sterilizer. These tubes were removed at intervals of one minute, and immediately placed in the incubator at 37°. The only tube which showed any development was that removed after an exposure of one minute.

The thermal death-point, as determined by Sternberg's method, was found to be 58°.

Effects of mercuric chloride. Ten silk threads, which had been saturated with a beef-tea culture of the bacillus, and then dried in sterilized dishes at room-temperature, were placed in a 1 : 1000 solution of mercuric chloride. Six of these threads were removed at intervals of one minute, placed in beef-tea-tubes, and kept in the incubator. The one that had been exposed to the mercuric chloride for only one minute showed a good growth after eighteen hours; the others,

not until thirty-six hours. Of the four other threads, one was removed after eight, one after ten, one after fifteen, and one after twenty minutes. The beef-tea-tubes in which these were placed remained sterile.

Eight threads were placed in a 1 : 5000 solution of mercuric chloride. The first was removed after two; the second, after five; the third, after eleven; the fourth, after fifteen; the fifth, after twenty; the sixth, after thirty; the seventh, after forty; the eighth, after sixty minutes. All of these were placed in beef-tea-tubes and kept at 37° in the incubator. The first three showed a good growth after eighteen hours; the fourth only after forty hours; while the others failed to show any development. A similar experiment was made with a 1 : 20,000 solution of mercuric chloride, but all the threads developed in the beef-tea.

Effects of carbolic acid. Threads similar to those employed with the mercuric chloride were sterilized on contact with 5, 4, and 3 per cent. solutions of carbolic acid; after two minutes, with a 2 per cent. solution, and after ten minutes with a 1 per cent. solution.

Differentiation from the bacillus coli communis. This bacillus was at first suspected of belonging to the colon group, and comparison-tests were made between the two. The most important results obtained in this comparison may be stated as follows: (1) The new bacillus fails to give the indol reaction. (2) Both coagulate milk, but the new germ acts more promptly than the colon bacillus. It may be stated here, parenthetically, that the colon bacilli used in this comparison were from two sources, one culture having been obtained some years ago from the laboratory of the Hygienic Institute at Berlin, while the other was separated from feces for the purpose of this comparison. (3) The pleasant butyric ether odor of milk cultures of the ice-cream bacillus is not developed in cultures of the colon bacillus in the same medium. (4) The new germ grows abundantly on carrots, forming a raised, creamy layer, and gives off a sour odor; while the colon bacillus grows much less vigorously and gives off no similar odor. On turnip, the new germ grows vigorously, forming a thick grayish layer, and this also develops a sour odor; while on the same medium the colon bacillus develops relatively feebly. On banana, onion, parsnip, and apple the new bacillus grows much more abundantly than does the colon bacillus. (5) Milk colored with rosolic acid

is decolorized much more quickly by the ice-cream bacillus than by the colon germ.

PATHOGENESIS. This germ is pathogenic to guinea-pigs, rabbits, cats, dogs, mice, and rats. Its virulence is increased by being carried through animals. In one series we employed fifty-one guinea-pigs, inoculating each with a culture made from the preceding animal. In all of this series the inoculations were made intra-abdominally. Of the culture with which we began, one cubic centimetre of a beef-tea growth twenty-four hours old was necessary in order to kill a guinea-pig of from two to three hundred grams within twenty-four hours; while of the cultures made from the animals near the end of the series, one-fiftieth of a cubic centimetre of like growth produced the same result. The decrease in the virulence of the germ when grown on the ordinary culture media is rapid, and the intensified virulence attained in the series referred to above disappeared in the third or fourth generation when grown on gelatin or agar. Milk seems to be the most suitable culture medium. We do not know that the germ multiplies more rapidly in milk than it does in beef-tea, but cultures in the former are more virulent than those in the latter. The suspension of the germ in sterilized milk when the inoculation is made renders its action more certain. One-fiftieth of a cubic centimetre of a beef-tea growth of our intensified germ added to one cubic centimetre of milk and immediately injected into the abdominal cavity of a half-grown guinea-pig invariably caused death within twenty-four hours; while an equal amount of the same culture added to beef-tea and injected into companion animals caused death only after a much longer period, and in some failed wholly to do so.

The germ taken from the exudate in the abdominal cavity and used directly for the inoculation of another animal is more virulent than if it be carried through a culture medium before the inoculation is made. The number of germs in one cubic centimetre of such a peritoneal exudate was determined in one instance and found to be 34,800,000. One one-hundredth of a cubic centimetre of this fluid injected into the abdominal cavity of a guinea-pig weighing 350 grams caused death within twenty hours, while one-half of this quantity failed to cause any visible effects. It will, therefore, be seen that the number of germs in the most virulent culture necessary to kill a half-grown guinea-pig, when injected intra-abdominally, is somewhere between

348,000 and half that number. Subcutaneously larger amounts of the cultures were necessary to cause death.

Experiments with Guinea-pigs. A few extracts from our record book will illustrate the action on guinea-pigs.

Aug. 1, 1895. Guinea-pigs Nos. 1 and 2 were treated intra-abdominally, each with one cubic centimetre of a beef-tea culture twenty-four hours old. The injection was made at 6 P.M. Both pigs were found dead at 7 o'clock the next morning. There was some gas in the subcutaneous tissue. The abdominal muscles were congested. The peritoneum was dotted with hemorrhagic spots. The cavity was filled with a reddish fluid. The liver was covered with a plastic exudate. The thoracic cavity contained some reddish exudate. The heart was in diastole and filled with blood. Cover-glass preparations made from the subcutaneous tissue, the peritoneum, the exudates of both cavities, and the blood of the liver, spleen, and heart showed the presence of the germ in pure culture.

Striking illustrations of phagocytic action may be obtained by injecting cultures, which are not sufficiently virulent to kill, into the abdominal cavity and killing the animal within the next two days. The following is an example: Guinea-pig No. 23, weight 233, was given 0.5 of a cubic centimetre of a beef-tea culture at 4 P.M., October 21, 1895. The weight, twenty-four hours later, had fallen to 214, and at the expiration of forty-eight hours to 198. The animal was killed at 4 P.M., October 23d. The muscles about the place of injection were highly inflamed. There was some wine-colored fluid under the skin. Germs were abundant in this fluid and in smears made from the subcutaneous tissue. Some of these preparations showed phagocytes filled with bacilli, but the most beautiful demonstrations of phagocytic action were found in smear preparations from the peritoneum. In these the phagocytes were innumerable, and many of them were crowded with bacilli.

The effects of a subcutaneous inoculation with a highly virulent culture is illustrated in the following: Guinea-pig No. 33, weight 207, received subcutaneously on the back one cubic centimetre of the fluid from the peritoneal cavity of No. 32 at 8.30 A.M., October 26, 1895. By 2 P.M. of the same day the weight had fallen to 200, at 10 A.M., October 27th, it was 188, and after death, at 2 P.M. of this day, the weight was 185. There was profuse diarrhœa during

the last twenty-four hours of life. The examination showed marked inflammation and infiltration subcutaneously over the entire trunk, under the skin of the abdomen, as well as under that of the back where the injection was made. Germs were found to be abundant both subcutaneously and within the peritoneal cavity.

The amount of fluid exudate found in the peritoneal cavity after both subcutaneous and intra-abdominal inoculations has been observed to be very variable. Guinea-pig No. 46, weight 230 grams, had, at 4 P.M., November 5th, intra-abdominally, one cubic centimetre of a milk culture six days old. It was found dead at 7 A.M., November 6th, and evidently death had occurred some hours before. The subcutaneous bloodvessels were much ingested, and we took from the peritoneal cavity seven cubic centimetres of a wine-colored fluid.

In some instances the peritoneal cavity has been found to be free from fluid.

Guinea-pigs have not been inoculated with this bacillus otherwise than subcutaneously and intra-abdominally.

Experiments with Cats. The following are some of our experiments made upon cats:

Cat No. 2 was inoculated intra-abdominally with 0.5 cubic centimetre of fluid taken from the peritoneal cavity of guinea-pig No. 11. The injection was made 3 P.M., October 12th. After one and one-half hours a profuse diarrhœa began and continued until death, which resulted at 11.20 A.M., October 13th. Examination showed marked inflammation of the peritoneum. There were no gross changes observable in the intestines.

Cat No. 6 had intra-abdominally, at 4 P.M., October 26th, one cubic centimetre of fluid from the peritoneal cavity of guinea-pig No. 31. The animal was not seen again until 8.30 A.M., October 27th, when it was found in collapse with a watery diarrhœa which had evidently been established some hours before. Death followed two hours later. The condition of the body was the same as that found in cat No. 2.

Cat No. 8 had intra-abdominally two and one-half cubic centimetres of fluid from the peritoneal cavity of guinea-pig No. 40 at 5 P.M., November 1st. Four hours later this animal was found to be vomiting and purging most profusely. It was dead at 9 A.M., November 2d. There was no inflammation at the point of inoculation

or in the peritoneum. Four cubic centimetres of fluid were taken from the peritoneal cavity. The heart was in diastole and filled with blood.

These cases show that when the inoculation is made intra-abdominally the action of the germ on the cat is prompt and vigorous. All the cats used were full grown.

Large quantities of cultures given by the mouth were without effect upon cats, as is illustrated by the following:

Gave to cat No. 6, through a stomach-tube, twenty-five cubic centimetres of a beef-tea culture nine days old. There was not the slightest evidence of the animal being in any way affected. Later this animal was inoculated intra-abdominally with the result already stated.

Cat No. 4 had by stomach fifty cubic centimetres of a beef-tea culture four days old; no effect.

Cat No. 5 had by stomach fifty cubic centimetres of an Uschinsky culture; no effect.

These results are interesting and are confirmatory of some experiments made by one of us some years ago in the study of certain samples of poisonous cheese. The smallest bit of this cheese induced vomiting in man, but a cat was kept for days with no other food than the cheese; she ate freely of this and was not affected thereby. We regret that we could find no young kittens upon which these experiments might be repeated.

Subcutaneously as much as four cubic centimetres of fluid from the peritoneal cavity of a guinea-pig, dead from the action of the germ, caused only a temporary local inflammation in the cat.

Two cubic centimetres or more of a beef-tea culture injected into the jugular vein in cats caused diarrhœa, prostration, and death.

Experiments with Rabbits. The following extracts from our record book illustrate the action of this bacillus on rabbits:

Rabbit No. 15 had injected into the jugular vein four cubic centimetres of fluid from the peritoneal cavity of guinea-pig No. 35. Death resulted five hours later. Post-mortem showed no fluid in the peritoneal cavity. The capsule of each kidney was distended like a bladder around the organ. Kidneys and liver were very soft and puffy. Smear preparations made from these organs showed myriads of germs. The heart was in diastole and filled with blood. The

pericardium contained some gas. It should be stated that this examination was not made for some hours after death, but the body lay during this time in the ice-box.

The above shows the effects of an intravenous injection of a large amount of a most virulent culture. With smaller quantities of ordinary beef-tea cultures the results are not so striking.

Rabbits Nos. 81, 82, 83, and 84 had each intravenously two cubic centimetres of a beef-tea culture twenty-four hours old. Nos. 81 and 84 died about twenty hours later, while the other two, although evidently quite sick for some days, ultimately recovered. In the examination of the dead ones the surface of the kidneys, on removing the capsule, was found in all to be dotted with hemorrhagic spots. The heart was in diastole and filled with blood, but neither the pericardium nor the renal capsules contained gas.

Intra-abdominally a virulent culture of the germ affects rabbits quite as promptly and seriously as it does cats. Rabbit No. 3 had 0.2 cubic centimetre of fluid from the abdominal cavity of guinea-pig No. 9. The rabbit was found dead twelve hours later, and evidently it had been dead for some hours. The subcutaneous bloodvessels were engorged. The peritoneum was only slightly inflamed, and the cavity contained four cubic centimetres of fluid.

In several instances we have seen rabbits lie for hours after an abdominal inoculation, in an apparently moribund condition, and then slowly recover. Repeatedly the janitor has reported the animal, either rabbit or guinea-pig, in a certain cage dead, and so it was apparently, but close examination has shown a faint motion of the heart, and in some cases, after the animal has remained in this condition for twenty-four hours, or even longer, it has slowly recovered.

Experiments with Rats. White rats succumb to both subcutaneous and intra-abdominal inoculations of from one to two cubic centimetres of a beef-tea culture. The post-mortem conditions are the same as those observed in guinea-pigs.

Experiments with Mice. White mice have not yet been tested with any thoroughness so far as the living germ is concerned, but they are most useful in the study of the action of the chemical poison. Our failure to test the action of the germ on this animal thoroughly is due to the fact that our stock of white mice has been very limited during the past year, and we have used the few we did have in other lines of

experimentation. However, two were inoculated subcutaneously with one drop each of an exudate from a rabbit, and were found dead after twelve hours. The post-mortem condition was the same as that observed in guinea-pigs inoculated in the same manner and with like cultures.

Experiments on Dogs. The following will illustrate the action of this bacillus on dogs, and show the differences between the effects of the intensified and the less virulent cultures:

An agar culture was made from one of the last of the series of fifty-one guinea-pigs already referred to. When this culture was eight days old the growth on the surface of the agar was rubbed up with two cubic centimetres of beef-tea and injected into the abdominal cavity of a St. Bernard dog weighing forty pounds. Within one half-hour the animal began to vomit and one hour later to purge. The vomiting and purging continued at intervals of fifteen minutes or longer for twenty-four hours. The retching movement of the abdominal muscles were frequent and powerful. For twenty-four hours longer the animal remained in a condition of collapse, and refused food. After this recovery slowly followed.

A second dog, weighing only eighteen pounds, received an agar culture which had not been intensified by being passed through animals. Twenty-five minutes later the dog vomited once, but further than this it was not affected.

THE POISONOUS CHEMICAL PRODUCTS. Our attempts to isolate the chemical poison or poisons of this bacillus have not been successful. However, we have ascertained some facts along this line, and these may be worthy of record.

Certain precautions must be observed by one who attempts to isolate the active, chemical constituents of bacterial cultures. The opportunities for falling into error are many, and the difficulties in the prosecution of the work are often great. We have met with some interesting experiences in this connection. In the first place, we hoped that we had in our new bacillus the generator of tyrotoxicon, and with the idea of determining this we rendered our filtered-milk culture alkaline, shook it with ether, allowed the ether to evaporate spontaneously and injected the residue dissolved in water into animals. The animals thus treated died very speedily, but, recalling the experience that one of us had in his study of tyrotoxicon, we tested the

residue from the ether alone, and found this to be most intensely poisonous. The residue from fifty cubic centimetres of this ether injected subcutaneously or intra-abdominally into a guinea-pig of from three to four hundred grams killed the animal within ten minutes. This ether is the product of a German manufacturer of good reputation. The residue from five hundred cubic centimetres of Squibb's ether produced no effect on animals. We found a recently received lot from another German firm, also free from harmful constituents. With these tested ethers the extractions, to be reported later, were made.

We have observed that some of the animals used in our experiments are very susceptible to the action of alcohol. Special attention must be given to this point in the administration of proteids precipitated by alcohol. These precipitates hold alcohol very persistently when dried in vacuo, and the amount of alcohol thus retained may be sufficiently large to markedly affect rabbits, rats, and guinea-pigs. These proteid precipitates may also, when apparently quite dry, contain enough ether, which we have sometimes used for washing out the alcohol, to affect the animals.

Hydrogen sulphide, when employed for the purpose of removing mercury, platinum, or other base used as a precipitant in cultures, is driven off with great difficulty, and it is a most potent poison to guinea-pigs.

Milk cultures, on account of their complex composition, are notoriously unsuitable for the isolation of bacterial poison. However, as these cultures of this bacillus are especially virulent, we have employed them, with some exceptions, to be stated later. Two-litre flasks, each containing one litre of sterilized milk, were inoculated with the germ taken directly from the peritoneal cavity of a guinea-pig. These flasks were kept in the incubator for thirty days. The contents were then filtered through paper. As soon as the pores of the paper were coated with the proteid part of the culture the filtrate became not only perfectly clear, but sterile. Thus the slow filtration through porcelain, practised in our first experiments, became unnecessary. From five to ten cubic centimetres of this filtrate injected into the abdominal cavity of full-grown white rats or half-grown guinea-pigs caused death within less than one hour. These filtered cultures were then distilled in vacuo at a temperature not above 40°,

until there remained in the retort not more than one hundred cubic centimetres. The distillate was acid with the pleasant odor of the original culture, and ten cubic centimetres failed to induce any symptoms in rats. Five cubic centimetres of the concentrated fluid in the retort killed rats within from five to ten minutes. This concentrated fluid, which was strongly acid, was shaken twice with double its volume of ether. On spontaneous evaporation the ether left a very small residue, which sometimes contained a few imperfect crystals. This residue injected into a full-grown rat killed it within four minutes. The above experiment was repeated many times, and, although the quantity of poison left on the evaporation was found to be variable, it was never altogether wanting. In some instances the residue from the ether consisted of a few drops of a brownish, oily semifluid. In others the residue was perfectly dry, and when examined under the microscope showed some granular matter mixed with a few imperfect and broken prisms. The removal of the poison from the concentrated fluid is imperfect and incomplete, as was shown by driving off the traces of ether from the fluid by keeping it for days in vacuo at 40°, and then injecting some of it into animals, when death resulted quite as promptly as before the extraction with ether was made. When this method was employed with the Uschinsky culture, the amount of the poison left on the evaporation of the ether was much less than that obtained from an equal volume of a milk culture. The animals died, but not until several hours after the injection. We have not been able to obtain enough of the poison to enable us to identify it chemically.

Many other methods of isolation have been attempted, but without success. The distillation was in several instances continued *in vacuo* until only a syrupy residue remained. This residue was extracted with absolute alcohol, which dissolves the poison, the alcoholic extract was evaporated, and this residue again treated with absolute alcohol. This was repeated as many as a dozen times and the alcoholic solution was finally precipitated with platinum chloride. This precipitate was crystallized, but was found to consist of a sodium salt.

In another experiment, the residue obtained after repeated extractions with alcohol was distilled *in vacuo* at a high temperature. At 130° a clear fluid passed over, but this consisted of glycerin containing only traces of the poison which was demonstrated by its action on animals, while the residue in the retort was found to be inert.

From the concentrated, filtered culture, when made alkaline with either ammonia or a fixed alkali, the poison is not removed by ether. This distinguishes this poison chemically from tyrotoxicon. Physiologically this poison is distinguished from tyrotoxicon by the more pronounced effect of the former on the heart, in which it resembles muscarin or neurin more closely than it does tyrotoxicon. Anatomically the two are unlike, inasmuch as the product of our bacillus induces marked congestion of the tissues about the point of injection or in the peritoneum when thrown into the abdominal cavity. Moreover, the intestinal constriction which was so universally observed in animals poisoned with tyrotoxicon has not been once seen in our work with this new germ and its poison, although it has been carefully looked for in the more than two hundred animals experimented with.

The poison is not removed from either acid or alkaline solutions with chloroform.

The following experiment was made in order to determine whether or not our bacillus elaborates a proteid poison or a toxin which is precipitated with the proteids. For this purpose an Uschinsky culture was selected, inasmuch as such a culture contains no proteids save those elaborated by the germ. A litre of an Uschinsky culture forty days old was filtered through porcelain in order to remove the germs. The clear, strongly acid filtrate was allowed to fall, drop by drop, into twice its volume of absolute alcohol. A flocculent, white preciptate fell and formed a thin layer on the bottom of the cylinder. This precipitate was collected on a filter and washed for two days with absolute alcohol. It was then dried between folds of filter paper and rubbed to a powder in an agate mortar. Twenty milligrams of this powder were suspended in water and injected into the abdominal cavity of a guinea-pig. The animal showed no effect of the poison at the time, but it died two days later. Post-mortem examination showed the same condition as had been observed after death from inoculation with the bacillus and after death from the poison extracted with ether. The peritoneum was highly congested, the abdominal cavity contained a reddish exudate, and the heart was in diastole and filled with blood. It may be that enough of the same poison, which is extracted with ether, had been carried down mechanically with a non-poisonous proteid, and had not been removed by the repeated washings with alcohol. If this be the case, or if there be two chemically distinct poisons, we

are not able to determine at present. The Uschinsky fluid which had been treated with two volumes of absolute alcohol, and from which the alcoholic precipitate had been removed as just stated, was concentrated *in vacuo* and the concentrated fluid was shaken with two volumes of ether, and the residue left on the evaporation of the ether injected into a guinea-pig caused death within four hours. Post-mortem examination showed the condition already described as due to the germ and the germ-free cultures.

By a mistake, in which a germ-free milk culture reduced to about half its volume was placed in a bottle labelled nucleinic acid, ten minims of this fluid were injected subcutaneously into a patient of about one hundred and fifty pounds weight. Within thirty minutes this person began to complain of dizziness. A few minutes later there was free vomiting. A little later the bowels moved freely. The vomiting and purging continued at intervals of a few minutes for four or five hours. Two hours after the injection the patient complained of deafness and responded only when the lips were placed near the ear and the words spoken in a loud voice. A little later there was wild delirium, the patient constantly attempting to get out of bed. Three hours after the injection the patient fell into a comatose condition. The feet and hands were cold and the radial pulse was imperceptible. Strychnin was given hypodermically and recovery followed slowly but completely.

Twelve hours after the injection all alarming symptoms had subsided, but it was two days before the patient was able to walk about the room. The next day the action of this fluid on guinea-pigs was carefully and repeatedly tested. The animals selected for this purpose weighed from one hundred and ninety to two hundred grams. Ten minims injected subcutaneously had no visible effect on them. One cubic centimetre induced only a slight and temporary effect. Within from five to ten minutes after such injections the animal retched a few times, but manifested no further symptoms. Two cubic centimetres caused death within from four to eight hours. These facts illustrate the difference in susceptibility to the action of this poison in man and guinea-pigs. Evidently our bacillus elaborates a poison of most potent action in man.

In our studies of the chemical poison we have evaporated the germ-free cultures *in vacuo* and at a low temperature. It must not be

inferred from this that higher temperatures quickly decompose the poison. Cultures heated in open dishes on the water-bath for hours, with the contents of the dish at 80° to 90°, do not lose their toxicity, and even brisk boiling over the naked flame for fifteen minutes is without appreciable effect. This shows that milk containing this poison, even after sterilization by heat, may not be altogether harmless. However, as we have already seen the germ is killed at comparatively a low temperature and by the sterilization of milk the further elaboration of the poison is prevented.

THE IDENTITY OF THE STREPTOCOCCI AND A DESCRIPTION OF AT LEAST ONE NEW VARIETY.

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THE study of the streptococci has a peculiar fascination for anyone familiar with bacteriological research, and it is of especial importance in the present condition of the work upon the "streptococcus antitoxine." Instead of being certain, as at one time we supposed we were, that the streptococcus of erysipelas, of puerperal fever, of septicæmia, and of many other processes, were all different because they produced different results, the latest opinion is strong that all these varying groups of symptoms are results of the activity of the same bacterium, altered so far as its virulence is concerned by conditions of surroundings and nutrition. That it is true that there is one streptococcus to which most apparent varieties are related, everyone may admit; but that there is one type to which all will return, if placed under proper conditions, does not permit of such ready assent.

No doubt the difficulties of the subject are much diminished if it be accepted, as some of the best observers have done, that this latter proposition is true, but I cannot yet do so. It does not seem possible to me to go so far as Peter, and to speak of the streptococcus as "le microbe à tout faire," but there is a strong probability that this bacterium—occurring very commonly on the healthy skin and mucous membranes—may take on, under as yet unknown conditions, an active degree of virulence, and become able to produce a large variety of changes in living tissues.

This variety of results produced by the same organism is something which experimenters have in the past been slow to recognize. Anthrax was the first disease to which a bacterium was definitely attached as an etiological factor, and just because this relationship *was* so definite,

and because the bacillus was so sharply outlined in all its characteristics, the feeling became widespread that *all* other processes must have just as definite a cause. This feeling was much strengthened by the results of the studies upon tuberculosis, the infectious wound diseases, and many others; but it has been weakened as investigation has become concerned with certain septic processes, and the knowledge of the differences between simple and mixed infections is being widely spread by the manifest clinical differences between simple and mixed diphtherias, data in regard to which are being so rapidly accumulated. So that now we are better able to understand the proposition that many differing processes may be the result of the activity of one and the same bacterium than was the case a number of years ago, but at the same time care must be taken not to err in the opposite direction.

The importance of this caution lies in the fact of the attempts being made to secure a streptococcus antitoxine, and the assumption made by most of the workers in this direction that an effective antitoxine can be prepared from any streptococcus, if only the proper methods of procedure can be determined—that is to say, that given a streptococcus from a case of erysipelas and of sufficient virulence, the antitoxine prepared from this culture will be equally effective against any other process due to a streptococcus invasion.

Of course, it is too early to speak with accuracy of the results obtained with the streptococcus antitoxine at all, but that the differences between the streptococci must be taken into account I believe to be indisputable. Some of my reasons for this are shown in the subject proper of this paper.

In making some investigations preliminary to an attempt to obtain some sort of streptococcus antitoxine, I have had the fortune to obtain several varieties of streptococci, but one of which is sufficiently worked out to admit of anything like a full description. And I wish here to acknowledge the very great assistance that I have had from Messrs. Flint, Frost, and Howland, students in the Harvard Medical School, who have given a large amount of time to the work, and without whose aid it could not have been carried on. I am especially indebted to the enthusiasm of Mr. C. P. Flint, who has done practically all of the later work.

The *streptococcus aureus liquefacians* was derived from a case of fatal puerperal septicæmia, of which the following is a brief history,

abstracted from that furnished me by the physician in whose practice the case occurred:

Mrs. S., primipara; labor on December 9, 1895; forceps delivery, with injury to the perineum; repaired with four stitches.

December 12th. No rise of temperature, but extreme pain and discomfort from the hemorrhoids, which were lanced and had the clots turned out.

13th. Lochia slightly offensive, but plentiful.

14th Chill in the morning and rapid rise of temperature. 8.30 P.M., uterus curetted with dull curette.

15th. Lochia plentiful, no odor. Erythematous erysipelatous blush over both nates extending from anus.

17th. Uterus thoroughly curetted; cultures and curettings both showed streptococci; cultures taken before and after curetting from the uterus, vagina, and the erysipelatous blebs.

19th. Cultures again showed streptococci.

19th to 24th. General prostration, profuse perspiration, tympanites, and delirium.

25th. Died in convulsions.

Autopsy, Dec. 26th, by Dr. A. K. Stone. Female, well nourished and well developed. Considerable subcutaneous fat. About the buttocks the skin thickened and congested. Near the anus a superficial ulceration covered with grayish membrane (wound left after removal of hemorrhoidal clots).

Thorax. Lungs normal, except some old adhesions to the costal pleura. Heart normal (except two or three subendocardial yellowish spots about one millimetre in diameter; fat in muscle).

Abdomen. Intestines distended with gas. About one litre of free fluid in the abdominal cavity; clear, except a few flakes of fibrin. Serous surfaces smooth and shining.

Kidneys. Normal in size, capsule easily removed; on section, some cloudy swelling of the cortex.

Liver. Normal.

Spleen. Slightly enlarged, soft, and friable; on section, soft and full of blood, so that the follicles were not easily made out.

Uterus. Enlarged so as to measure 6–8 cm. across between the cornua; on section, the surface clean, except in both cornua there remained portions of a thick, gray membrane about 1 cm. in diameter; in the cervical canal several places where the wall showed hemorrhagic infiltration extending to a depth of about 2 cm.

Cultures taken from the abdominal fluid and the various organs all showed the streptococci of which I wish to speak to-day.

The "streptococcus aureus liquefacians" is the name that I have given to this bacterium provisionally, and it appears to be as fitting a designation as can be selected. In the original microscopic prepara-

tions it appeared as short and long chains, containing from four to eight cells, of the size of the staphylococci. The cultures showed the same appearance except that many of the chains were much longer.

The growth upon gelatine in plates appears after forty-eight hours as fine, sharply defined points, with no liquefaction; but after seventy-two hours the colonies are larger, of an orange-yellow color and surrounded by a liquefied zone. In gelatine tubes, after twenty-four to forty-eight hours, the colonies appear as minute whitish points along the needle track. In from forty-eight to seventy-two hours there is a golden-yellow color to the colonies, and liquefaction extends along the whole of the needle track; is bulb-shaped at the bottom, and has a thick, granular, and opaque sediment settling to the bottom.

On agar there is a translucent whitish growth along the needle track, made of small discrete colonies that later coalesce. There is a faint yellowish color at the thicker part of the growth which never becomes as marked as on blood-serum, and is hardly apparent on the remainder of the colony.

On potato, somewhat elevated moist colony taking on a yellow color after twenty-four hours, growing very slowly except at blood temperature.

On blood-serum the growth occurs as a thick layer with distinct colonies on the edges, the single colonies being as large as a pin's head. The young colonies are white, but within forty-eight hours the growth takes on a deep orange color.

In bouillon produces a marked cloudiness of the medium or adheres to the sides of the tube in large and small flakes.

In litmus-agar turns blue litmus to red in twenty-four hours.

On egg-albumin appears in fine white colonies that later turn of an orange color.

On yolk of egg the appearances are the same as upon egg-albumin.

Grows best at the body temperature.

Its growth is rapid at this temperature, and slow at lower ones.

No gas-production has been observed.

Is facultative anaërobic.

No spore-production has been observed, unless the occurrence of large cells in the course of the chains be such; but cultures retain their vitality for at least three months.

Liquefies gelatine slowly.

Stains with any of the aniline colors, and with Gram. Produces a golden-yellow pigment.

Guinea-pigs are susceptible only in very large doses, the virulence diminishing very rapidly in these animals. White mice are very slightly susceptible. Rabbits die in from fifteen to twenty hours after a subcutaneous injection of 0.1 c.c. of a twenty-four-hour bouillon culture.

This degree of virulence is very remarkable, and the results are those of pure septicæmia; there is not at any time any appearance of suppuration; on post-mortem examination a slight congestion of the internal organs, a small amount of serous fluid in the peritoneal cavity, and a small patch of reddening at the point of inoculation are all that are visible. The microscope and cultures, however, show the presence of large numbers of the bacteria in the peritoneal fluid, the blood, and at the point of inoculation.

The puzzling characteristic of this organism is that as the degree of virulence has been increased by constant and rapid transmission through animals (rabbits), the chains have become shorter and shorter, until now there is no apparent difference under the microscope between this and the staphylococcus pyogenes aureus—that is to say, that the original bacterium has lost its streptococcus form under the intensifying process. So that it is useless to attempt to show cultures under the microscope to prove the existence of the chain-formation. At the same time this chain form returns after a few generations have been passed through fluid culture-media, and presumably with an increasing diminution of virulence.

The study of this form is manifestly incomplete, and this communication is made entirely as a preliminary one; but unless the observations are wholly wrong, they furnish to my mind very complete evidence that it is a matter of considerable doubt whether all streptococci are the same, even for the purposes of producing a streptococcus antitoxine.

DISCUSSION.

DR. STERNBERG: A streptococcus which liquefies gelatin and produces yellow pigment is certainly quite distinct from the ordinary streptococcus of puerperal infection. The fact that this organism at first formed long chains,

and that in the course of cultivation the chains became shorter, is just the reverse of what was found by von Lingelsteim in regard to the streptococci studied by him. His streptococcus brevis was non-pathogenic, and the streptococci in long chains he considered pathogenic. I do not think that subsequent researches have justified his conclusion that the streptococci can be divided into two principal varieties, one long, the other short, one being pathogenic, the other much less so. The streptococcus described by Doctor Ernst seems to be quite different from any heretofore reported.

DR. A. C. ABBOTT: The controversy concerning the identity of streptococci has been directed to those having the same morphological and cultural characteristics, but differing in being associated with different pathological conditions.

As the organism described by Dr. Ernst has little or nothing in common with streptococcus pyogenes or erysipelatus I do not see that it has any important bearing upon the disputed point.

DR. BOLTON: I have no doubt that this is a new streptococcus. At the same time I would like to say that Cruikshank, some time ago, in studying the staphylococci, found that they so often appear in chains that, in one edition of his book, he discards the name staphylococci, and calls the whole of them streptococci—streptococcus pyogenes albus, aureus, and citreus. Staphylococci probably do sometimes grow in chains.

DR. ERNST: Regarding Dr. Abbott's remarks, I would like to say that the point that it seemed necessary to me to make was more in answer to Marmoreck's assertion in his work on the streptococcus antitoxine, that the immunity obtained by one streptococcus is effective as against any other streptococcus. If there are streptococci like this, which are possessed of such extreme virulence, then the antitoxine prepared from it, by all that we know, must be something different from the antitoxine derived from the ordinary bacteria of erysipelas or septicæmia.

In regard to Cruikshank's assertion, all that I can say is that I have worked a long time over a great many varieties of staphylococci, and have never seen them take on the chain formation as this does. I readily grant that the cultures are almost indistinguishable from the staphylococcus pyogenes aureus, but I have seen cultures of that organism for years, and from all sorts of sources, and used them through all sorts of experiments, and I have never seen them take on the chain formation.

THE CONDITIONS WHICH INFLUENCE THE APPEARANCE OF TOXIN IN CULTURES OF THE DIPHTHERIA BACILLUS.

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(*From the Pathological Laboratory of the State Board of Health of Massachusetts.*)

ANY positive additions to our knowledge of the formation of poisons or toxins by bacteria, however slight, are of considerable importance because the explanation of the nature and of the action of antitoxins seems likely to be delayed until that of the toxins is forthcoming. It is from this point of view that I present some facts, in part already published by others, concerning those circumstances which favor or oppose the accumulation of toxins in culture fluids. We have no reason to believe that the action of diphtheria bacilli on mucous membranes differs from that manifested in cultures. A complete knowledge of the favoring and inhibiting influences upon toxin formation might possibly furnish us with antitoxic weapons other than those now contained in the antitoxic serum of the horse.

In the course of work directed to the production of antitoxin since July, 1895, my attention has been centered upon the conditions which control the accumulation of diphtheria toxin in ordinary bouillon.

These conditions are: 1, the presence of muscle sugar in the beef used; 2, the oxygen supply; and 3, the manner in which the bouillon is prepared, with special reference to the peptone. These conditions are so interdependent that a separate consideration of each one is quite out of the question. I shall, nevertheless, endeavor to group the facts under these heads as far as possible.

THE MUSCLE SUGAR.

It is an interesting fact that the information requisite for the production of strong toxin appeared only late in 1895, and that before

this time chance reigned supreme in the bacteriological laboratory on this subject. And yet the facts necessary for a comprehension of the mysterious variability in the amount of toxin accumulated were at hand. In 1888 Roux and Yersin[1] stated that the reaction of the bouillon in which diphtheria bacilli were multiplying became first acid, then alkaline, and that the toxicity of cultures begins with the alkaline reaction. In 1893[2] I pointed out that if diphtheria bacilli be cultivated in bouillon free from muscle sugar or nearly so, the reaction remains alkaline from the start. Here was the information necessary to show that the presence of muscle sugar was not an indifferent matter and that the variation in the quantity found from animal to animal would explain not only the variation in the amount of toxin produced from one lot of bouillon to another, but also from one flask to another of the same bouillon. When I began the preparation of toxin in July of 1895, no explanation of the troublesome variability of the toxic power of cultures had appeared, although I had previously urged several to examine into its relation to the fluctuations of sugar in the beef. I at once began to examine every lot of bouillon in the fermentation tube as to the relative amount of muscle sugar present.[3] This was recorded and its relation to the toxin noted. Early in November I had tested a sufficient variety of broths to become convinced that the amount of toxin decreased as the presence of muscle sugar grew larger, and that the best toxin was obtainable only from beef nearly free from this substance. At this time was published a review of a dissertation by Van Turenhout[4] on the preparation of diphtheria toxin, which took the same ground. Some time after Spronck,[5] under whom this dissertation had been prepared, went over the same ground in another publication. Spronck brings the quantity of toxin found in bouillon in direct relation to the muscle sugar present and describes three types of growth, one in bouillon free from muscle sugar, which remains alkaline and produces much toxin; one in bouillon which contains a little sugar, becomes first acid, then alkaline, and produces less toxin; and one in

[1] Annal. de l'Institut Pasteur, 1888, p. 629.

[2] The Wilder Quarter-century Book, p. 224.

[3] The diphtheria culture with which the work to be described was done was kindly sent to me by Dr. W. H. Park. As it maintained its toxin-producing power apparently unimpaired I restricted my studies to it, thus eliminating any variability inherent in the bacilli themselves.

[4] Abstract in Centralblatt f. Bakteriologie, 1895, xviii. p. 295.

[5] Annal. de l'Institut Pasteur, 1895, p. 758.

bouillon containing much sugar in which the acid reaction appears promptly, remains permanent, and in which little or no toxin is produced.[1] This is the gist of the matter as regards the influence of muscle sugar. At the beginning of this year Park and Williams[2] published experiments confirming Spronck's position, and presented other facts of interest which I shall refer to again.

In order to know precisely in what condition the bouillon was for the production of toxin, I tested it in the following way: Several fermentation tubes were filled with the bouillon in preparation and sterilized. One was then inoculated with some acid-producing bacterium. I used *B. coli*, as it is easy procurable. Other acid-producing bacteria can also be used, for the small quantities of muscle sugar present in bouillon led with all bacteria tried to the same degree of acidity. A simple inspection of the tube from day to day gives sufficient information of the muscle sugar present. If the closed branch of the fermentation tube remains clear, sugar is entirely absent. If it becomes clouded, the cloudiness increases in density with the quantity of sugar present. If a little gas appears, the quantity may be still larger in proportion to the gas accumulated. In all cases the open bulb must become clouded or turbid, otherwise the bouillon is unfit for the multiplication of bacteria. At the end of a week the acidity is determined with a $\frac{1}{20}$ normal NaHO solution and phenolphthalein as an indicator, according to the suggestions made by G. W. Fuller.[3] In order to get uniform results I allow the titrated fluid to grow cold, when the pink color will be much stronger. The tints in different dishes may then be compared and more alkali added if the tint is too feeble, or some $\frac{N}{20}$ H_2SO_4 added if the color is too deep.

In former publications I pointed out that the alkali-producing power of facultative anaërobic bacteria was exercised only in the presence of oxygen in the open bulb of the fermentation tube. In the closed branch this power is repressed and the acid-producing power unchecked. The difference between the bouillon in the closed and the open branch of this tube may be equivalent to as much as 3

[1] Spronck was evidently not acquainted with the published observations of the writer on the variations of the quantity of muscle sugar in beef.

[2] The Journal of Experimental Medicine, i. 1896, p. 164.

[3] The Journal of the American Public Health Association, 1895, p. 386.

per cent. of a normal acid solution.[1] Hence by determining the acid in the closed branch of this tube we obtain an accurate idea of the quantity of muscle sugar originally present.

When the difference in acidity between the sterile bouillon and the fluid in the closed branch after a week's growth is only a few tenths per cent. the sugar is present in traces only, and a strong toxin may be expected. When the difference is much greater and the total acidity rises to 3.5 per cent. alkali (35 c.c. normal acid per litre)[2] the bouillon will probably yield no toxin. Between these two extremes all variations are met with and all degrees of toxicity of the culture as indicated by the following illustrations:

Bouillon No. 30. Final acidity to phenolphthalein after sterilization equivalent to 1 c.c. normal alkali per hundred c.c., or 1 per cent. In fermentation tube with *B. coli* and *B. cloacæ* after eight days in thermostat, the closed branch has an acidity of 1.4 per cent. The acidity was thus increased by only 0.4 c.c. normal alkali per centum, or 4 c.c. per litre. The bouillon yielded a very strong toxin.

Bouillon No. 36. Final acidity equivalent to 1.4 per cent. normal alkali. In two fermentation tubes inoculated with *B. coli* acidity in closed branch rose in six and nine days to 3.4 per cent. and 3.6 per cent. respectively. The acidity had thus increased 2 per cent., or 20 c.c. per litre. Toxin practically absent on the 11th day.

Bouillon No. 32. Initial acidity, 1.00 per cent. *B. coli* acidity, 1.85 per cent. Increase 0.85 per cent. Toxin strong.

Bouillon No. 64. Initial acidity, 0.68 per cent. *B. coli* acidity, 2.16 per cent. Toxin medium.

Bouillon No. 72. Initial acidity, 1.09 per cent. *B. coli* acidity, 2.60 per cent. Toxin feeble.

[1] Another preliminary method may be used when the more accurate titrations cannot be carried out. In a recent publication (Centralblatt für Bakteriologie, 1896, xix. p. 181), I pointed out that litmus is reduced in presence of muscle sugar when boiled with it. The reduction is manifest only in the fermentation tube, because in tubes open to the air oxidation hides the process. When bouillon is boiled in the fermentation tube with enough litmus to give it a distinctly blue or violet color, according to the original color of the bouillon, the color in the closed branch will be completely removed when muscle sugar is present in considerable amount. In bouillon free from it no reduction will take place. In bouillon containing a little only a slight discoloration will ensue.

[2] The notation employed throughout this paper to indicate degree of reaction is based upon the phenolphthalein neutral point, and quoted in c.c. of normal sodium hydrate solution per hundred c.c. bouillon. Thus an acidity of 1 per cent. means that 1 c.c. of normal alkali solution is required for every 100 c.c. of bouillon to produce a feeble pink color with phenolphthalein. This would be equivalent to 10 c.c. per litre. Since a fluid neutral to litmus requires about 15 c.c. alkali per litre, or 1.5 per cent. alkali to bring it to the phenolphthalein neutral point, a bouillon quoted as having an acidity of 1 per cent. in these pages is alkaline to litmus by 0.5 per cent. alkali.

Bouillon No. 73. Initial acidity, 1.22 per cent. *B. coli* acidity, 2.40 per cent. Toxin feeble.

Bouillon No. 76. Initial acidity, 1.00 per cent. *B. coli* acidity, 1.41 per cent. Toxin strong (decomposed beef).

Bouillon No. 78. Initial acidity, 1.50 per cent. *B. coli* acidity, 2.40 per cent. Toxin strong (decomposed beef). (Initial acidity reduced to 0.8 per cent. before inoculation.)

Bouillon No. 79. Initial acidity, 1.6 per cent. *B. coli* acidity, 1.8 per cent. Toxin very strong (decomposed beef).

Bouillon No. 81. Initial acidity, 0.8 per cent. *B. coli* acidity, 3.0 per cent. Not yet used.

The employment of phenolphthalein has been so satisfactory that the use of litmus has been entirely abandoned. The objections urged against the former are largely obviated by vigorously boiling the bouillon before titration, and adding the alkali while hot.

The total acidity of the bouillon might also be estimated in test-tubes inoculated with the diphtheria bacillus itself, but the other method is more accurate since the time when the reaction changes in open tubes is not determinable.

In tracing the relation between muscle sugar and toxin in bouillon cultures I endeavored to eliminate the vague distinction of acid and alkaline by a quantitative determination of the acids formed. For this purpose 5 c.c. were withdrawn from cultures from time to time, brought to the boiling-point, and titrated against a 1 : 20 normal solution of sodium hydrate with phenolphthalein as an indicator.[1] The results of such determinations are plotted on the accompanying charts. The work was frequently embarrassed by the accidental contamination of the flasks, hence the titrations were not made quite as often as one should wish. The curves of infected flasks are omitted with one exception. The irregularity of the curves is probably, to a certain extent, due to the handling and consequent disturbance of the flasks. The titrations are indicated by black dots. The curves were constructed by connecting these.

Chart I. epitomizes a preliminary study of the relation between sugars and acids formed. The bouillon used contained very little muscle sugar. It was sterilized in large test-tubes, which were kept in an inclined position after inoculation to expose a large surface of the culture fluid to the air. It will be noticed that neither lactose nor

[1] G. W. Fuller, loc. cit.

saccharose is acted upon by the diphtheria bacillus, the curve of the tubes containing 1 per cent. of these sugars closely approximating that of the control tube. The addition of dextrose changes the curve very markedly. The acid reaction, formed promptly in all dextrose bouillon, disappeared after a certain number of days when 0.1 and 0.125 per cent. sugar was used. With 0.2 per cent. there comes a parting of the ways. The acid is formed in larger quantity, and the culture does not recover its alkaline reaction. With percentages of dextrose higher than this the curves closely follow one another. The amount of acid formed is quite large. In several tubes there was as much as 7 per cent. of the alkali needed to the phenolphthalein zero-point. Taking as a starting-point the litmus neutral point at 1.5 per cent., the largest amount of acid accumulated would be equivalent to 0.2 per cent. solution of hydrochloric acid.[1] Of a variety of bacteria tested, I have found the diphtheria bacillus to bring about the largest accumulation of acid. Thus the typhoid, hog-cholera, and colon bacilli produce a maximum acidity equivalent to only 5.5 per cent. of normal alkali solution.

Chart II. furnishes a somewhat closer analysis of production of acids from dextrose. The bouillon chosen was practically free from muscle sugar, as shown by the fermentation test and curve of flask 1, the control culture. The initial acidity was quite low, thus giving the culture a good start at the outset. The quantity of dextrose was added as follows:

	Per cent.
To flask 1	None.
" 2	0.1
" 3	0.12
" 4	0.13
" 5	0.14
" 6	0.15
" 7	0.16
" 8	0.17

The bouillon was put into 500 c.c. Erlenmeyer flasks, 250 c.c. into each flask. The layer of fluid was 3 to 4 cm. deep. The dextrose was kept in a sterile 16⅔ per cent. solution, the strength having been carefully determined with Fehling's solution. Flask No. 5 became contaminated, but its curve does not depart from that of the pure cultures. The quantity of acid produced varied with the amount of

dextrose added. The acute form of the downward loop of the curves, the promptness with which the acid disappeared, in other words, is noteworthy when compared with the wider straggling curves of Chart III.

The curves marked *A* on this latter chart represent ordinary peptone bouillon to which no dextrose had been added. The difference in the size of the downward loop of the individual curves was due to the fact that the surface of the bouillon varied from flask to flask according to the numbers, while the composition was the same in all.

These charts show how rapidly the acid reaction is brought about in presence of dextrose. This rapidity suggests strongly the action of a ferment by which the sugar is decomposed. The return to the alkaline reaction is slower, often greatly delayed when the amount of acid formed reaches a certain limit, and is probably due to phenomena of growth and multiplication in the course of which the acid is oxidized and used as a food.

The action of diphtheria bacilli on dextrose having been made clear, it now remains to trace the influence of the acids formed on the bacilli themselves. These seem to thrive best between an acidity of 1.5 to 0 per cent., estimated from the phenolphthalein neutral point. The presence of muscle sugar beyond 0.15 per cent. increases the acidity to such a degree that a cessation of growth becomes manifest. Under the influence of the acid medium, the bacilli settle to the bottom, coat the glass with a peculiar thin, cloudy deposit not easily removed by shaking. The growth thereby comes to a premature close. When muscle sugar is present in traces only so that the depression of the reaction curve is but slight, a vigorous growth begins at once in the form of a surface membrane or pellicle which in twenty-four to forty-eight hours covers the entire fluid. The prompt formation of the membrane has puzzled me for some time. I am inclined to attribute it to the reaction of the fluid. According to Chittenden and Gies,[1] mucin in acid solution sinks to the bottom. When the fluid is neutralized the mucin swells and rises to the top. The outer envelope of most bacteria appears to be composed of a substance which behaves like mucin, according to Welch, during the process of staining. Pellicles appear on bouillon cultures of many

[1] The Journal of Experimental Medicine, 1896, I. p. 186.

bacteria after weeks of standing when the fluid has become alkaline.[1] The diphtheria bacillus is probably no exception to the rule. At any rate the membrane seems linked to an acidity less than 1.5 per cent.; *i. e.*, an acidity which is really neutral or alkaline to litmus. A membrane is, according to my observations, almost proof positive that the acidity is below a certain limit. In exceptional cases when the initial acidity of the culture fluid is purposely made very low (0.5 to 1 per cent.) a membrane forms at the very outset during the period still alkaline to litmus, but as the acidity develops this membrane fails to grow, and partially or wholly disappears. When the acidity is but temporary, owing to the vigorous oxidation of the acids carried on by the pellicle, the membrane may survive the acid period, as was the case in the flasks of Chart II. A similar relation of membrane-formation to an alkaline reaction has been noted by Park and others.

THE RELATION OF DIPHTHERIA BACILLI TO OXYGEN.

Diphtheria bacilli are eminently but not exclusively aërobic. They thrive best in thin layers with a free exposure to the air, and the alkaline reaction appears only when the layer is not too deep. Roux and Yersin recognized this fact in their earlier work, but they went to extremes when they considered it necessary to keep a continual current of air passing through the culture flask. From their statement it is not clear whether they thereby intended to bring about an alkaline reaction by an "oxidation of the nitrogenous bodies" independently of the bacteria, or whether they thought it necessary to supply the very modest demands of the bacteria in such liberal measure. I have not seen any indication of the oxidizing action of the air independent of the bacteria, so that a little air is *à priori* better than much air. The latter appears to disturb the surface membrane, and is therefore rather harmful than otherwise.

Numerous voices have been raised lately against the practice of drawing air through culture flasks, but it is well to warn here against the possible tendency of neglecting the oxygen supply altogether. Chart III. shows the effect of varying the surface exposure of the fluid. The return to the alkaline condition is much slower when the

[1] Bacteria like those of the rabbit-septicæmia group become very viscid on alkaline nutrient agar after a time.

surface is small. The same fact may be demonstrated in the fermentation tube. In one branch where only a limited amount of air is admitted, the acidity of the culture fluid may be twice as great as in the open bulb four to five days after inoculation:

Peptone Bouillon No. 51. Final acidity 0.75 per cent. Fermentation tube, inoculated with *B. coli*, examined after seven days. Bulb feebly alkaline. Branch requires 2.4 per cent. alkali.

Fermentation tube with 50 per cent. air in closed branch inoculated with diphtheria bacillus. After ten days, bulb requires 1.1 per cent. alkali. Branch requires 2.5 per cent. alkali.

The increase of the alkaline reaction in the presence of air is probably due to the oxidation of the acids formed by the bacilli out of the sugar and may be supplemented by the formation of $(NH_4)_2CO_3$. The curves presented on the charts represent fixed alkali left after the culture fluid had been kept at the boiling-point for about one minute.

Maassen,[1] in a recent study of the action of bacteria upon organic acids, denies to the diphtheria bacillus the power to use them. Only one exception, that of malic acid, is recorded. The apparent conflict between his results and those indicated by the curves is due to the concentration of the acids used by him. They were added so as to make a $\frac{1}{10}$ normal solution. If we allow, according to the curves on the charts, the maximum strength of acid capable of being consumed by the diphtheria bacillus to be 40 c.c. per litre of a normal solution, this concentration would be equivalent to $\frac{1}{25}$ normal solution only. His amounts were thus $2\frac{1}{2}$ times the maximum quantity capable of being oxidized by the bacilli.

The foregoing pages show that muscle sugar must be present only in traces up to 0.05 per cent., and that a large surface exposure to the air must be provided to favor to the highest degree the multiplication of diphtheria bacilli. Other things being equal, the more abundant the growth the greater the accumulation of toxin. The necessity of in some way getting rid of the muscle glucose to insure a toxic bouillon of maximum concentration becomes evident. The means to suppress or circumvent it are various: 1. We may allow the beef to putrefy according to Spronck's suggestion. 2. We may add $CaCO_3$ to the bouillon to neutralize the acid as it is formed, also first suggested by Spronck in connection with diphtheria cultures. 3. We may allow

[1] Arbeiten a. d. Kaiserlichen Gesundheitsamt, 1896, xii. p. 340.

some inoculated acid-producing organism, or the diphtheria bacillus itself, to split the sugar, and then after four or five days proceed to neutralize the acid formed, add the peptone, and resterilize, as is shown by the following trial with 1 per cent. peptone bouillon No. 73, whose initial acidity was 1.22 per cent. and *B. coli* acidity 2.4 per cent. Control cultures with peptone added same as below gave only a feeble toxin:

March 22*d*. Litre flask with 500 c.c. in a rather deep layer of 4.5 cm., inoculated with an acid-producing coccus.

23*d*. Acidity, 2.06 per cent.

24*th*. Acidity, 2.10 per cent.

26*th*. Acidity, 2.55 per cent.

27*th*. Acidity, 2.23 per cent.; 1 per cent. peptone, and 9 c.c. Na_2CO_3 (normal solution) to an estimated alkalinity of 1 per cent. added, steamed three times.

April 3*d*. Inoculated with diphtheria culture.

4*th*. Membrane formed.

7*th*. Membrane dense.

10*th*. Acidity 0.4 per cent. Control culture pure. Guinea-pig of 300 grams killed by 0.05 c.c. in twenty-four to twenty-eight hours.

4. We may begin with a high initial alkalinity according to Park. Of these methods I have given a fair trial to all, and consider the preliminary putrefaction of beef by all means the best. The addition of $CaCO_3$, combined with a low initial acidity of 1 per cent., has also yielded in my hands fairly satisfactory results. The preliminary use of acid-producing bacteria has likewise proved successful. The suggestion of Park to begin with a high alkalinity has not been successful in my hands with bouillon containing the average amount of muscle sugar. I have lowered the acidity of the bouillon to 0.5 and 1 per cent (probably equivalent to Park's 10 and 5 c.c. additions of normal alkali per litre) without enabling the culture to rally from the depression produced by the acid formed. I would, therefore, recommend that the beef be allowed to decompose for three or more days, and then be made into bouillon. Since the results of the decomposition are variable, the bouillon should be tested before use in the fermentation tube to determine how much acid is still likely to appear. The final reaction may then be adjusted by the addition of normal sodium hydrate or sodium carbonate, in proportion to the amount of muscle sugar still remaining. If the increase in acidity produced with

B. coli, for example, is not more than 0.2 to 0.8 per cent., the initial acidity of the bouillon may be chosen at 1 per cent., or 10 c.c. per litre. In this way a vigorous surface growth is at once established, and within eight or ten days the reaction will have swung up to and even several tenths beyond the phenolphthalein neutral point, and the largest amount of toxin producible by the bacillus in hand will be realized within this time. This may be illustrated by the following extract from my notes:

Toxin 1*E*. Made from decomposing beef, 1 per cent. peptone added *after* boiling and filtering of beef-juice, and enough alkali (Na_2CO_3) to bring acidity down to 0.8 per cent. Final acidity after sterilization 1 per cent. *B. coli* acidity 1.4 per cent. Gives promise of strong toxin. Divided into three portions before sterilization, each treated somewhat differently.

Toxin 1*Ea*. Large Fernbach containing 900 c.c. Tubulated rubber stopper in it for air suction. April 1st, 1 per cent. peptone added in sterile 20 per cent. solution, raising acidity to 1.5 per cent.

April 3*d*. Inoculated with about ½ c.c. forty-eight hours' bouillon culture diphtheria.

4*th*. Membrane present. Air drawn through slowly for one-half hour.

9*th*. Air drawn through daily for a short time. Membrane rifted, and in some places missing.

10*th*. Acidity 1.15 per cent. Control culture pure. Guinea-pig of 340 grams killed by 0.05 c.c. of filtered fluid in twenty-eight to thirty-three hours. Minimum fatal dose probably 0.015 c.c.

Toxin 1*Eb*. Tubulated Fernbach containing 600 c.c. Treated as 1Ea save that air is not drawn through and that acidity of added peptone is neutralized by 3 c.c. sterile NaHO solution, bringing the bouillon to an acidity of 1 per cent. Membrane vigorous on second day. On seventh day reaction is beyond phenolphthalein point by 0.1 to 0.3 per cent. Control culture pure. Guinea-pig of 385 grams killed by 0.05 c.c. in twenty-eight to thirty-three hours.

Toxin 1*Ec*. 600 c.c. in tubulated Fernbach. No air, no additional peptone or alkali. Membrane present on second day and remains. On seventh day reaction like that of 1Eb. Guinea-pig of 327 grams killed by 0.05 c.c. in twenty-one to twenty-three hours.

The presence of muscle dextrose in beef in variable quantity is thus largely to blame for the variation in quantity of toxin accumulated in cultures. We may obtain beef in which only traces of sugar are present and which furnishes a toxin of great concentration. We may, the very next time, obtain beef in which the sugar is present in such quantity as completely to inhibit after a few days all further multipli-

cation. Having tested all beef made into bouillon for more than three years, I was interested in looking over my notes to see that the beef obtained in Washington, D. C., contained a uniformly larger quantity of muscle sugar than that obtained in the vicinity of Boston, Mass. Hence, other things being equal, it would be much more difficult to obtain diphtheria toxin in one place than in the other. Now that means are at hand for removing the muscle sugar this difference would no longer be of any importance. Similar difficulties may have existed in other places, otherwise the chronic wail of some persons over the weakness of the toxin produced by them can scarcely be accounted for. I have also noticed that in the vicinity of Boston much less muscle sugar was contained in beef in the winter than in the fall and spring. During the winter the quantity present was rarely sufficient to lead to the formation of gas, and gave rise in *B. coli* cultures in fermentation tubes to a maximum acid production of 1 to 1.5 per cent. over and above the original acidity of the bouillon. In the warmer season this rose to 2 and 2 5 per cent. above the original acidity. This points to a post-mortem production of muscle sugar during warm weather, as has been generally held. My observations lead me, however, to add another element, the condition of the animal which predetermines the accumulation of glycogen, or that substance transformable into muscle sugar. The whole subject is worth the renewed attention of physiological chemistry aided by bacteria, as the most delicate reagents for sugar.

It must not be inferred from the foregoing that dextrose is wholly inimical to the diphtheria bacillus. Small quantities are favorable, for I have added 0.05 per cent. to bouillon which contained only traces of it, and have still obtained toxin of maximum strength. In Löffler's serum the addition of the prescribed 1 per cent. dextrose to the bouillon, making a 0.25 per. cent. solution for the whole serum mixture, is decidedly stimulating to the growth. Cultures of the same organism, one on Lœffler's serum with dextrose, the other on the same serum without dextrose, are quite different in appearance. The former is eventually much richer in growth, and its color is pale-yellowish instead of white. The reason for this is probably to be found in the exclusive surface growth which enables the bacilli to oxidize and assimilate the sugar present.

THE PEPTONE BOUILLON.

The muscle glucose has only a certain practical interest for us in that it is the cause of the feeble accumulation of toxin. It does not play much of a *rôle* in the biology of the diphtheria bacillus, probably because the latter prefers a strictly aërobic existence. The toxin itself is directly dependent on the peptone added, to which we shall now briefly turn our attention. Smirnow[1] states that the specific poison of diphtheria is developed only upon serum-albumin and albumoses. Upon globulin the bacilli multiply, but produce no toxin. He furthermore states that the strength of the poison varies in different media, being weaker in horse than in beef bouillon, and strongest in veal bouillon. The latter statement was written before the antagonistic action of muscle sugar became known, and is evidently true only in so far as the muscle sugar varies. V. Dungern[2] increased the virulence of diphtheria bacilli in peptone bouillon to which he had added ascites fluid. This virulence subsequently persisted in ordinary peptone bouillon cultures. Whether he used a different bouillon for these latter tests is, of course, not stated. Different amounts of peptone have been used by different investigators. Roux and Yersin used 2 per cent. Park and Williams mention the use of peptone in various strengths from 1 to 4 per cent., all of which yielded strong toxin, although occasionally the 1 per cent. peptone yielded the strongest toxin. How can we account for these vagaries?

My own work has been carried on almost exclusively with peptone bouillon. In one case dog's serum added to bouillon in 5 per cent. solution yielded no toxin. In one trial with Dunham's solution, containing 2 per cent. peptone, the growth was so feeble that the test on guinea-pigs was abandoned. The difference between 1 and 2 per cent. peptone bouillon as toxin-producers impressed itself upon me early in the work. Nevertheless, now and then, even 2 per cent. failed to yield toxin in sufficient quantity. In looking over my notes I noted that when a 2 per cent. peptone bouillon was made at the outset it yielded far less toxin than where 1 per cent. was added subsequently in sterile solution to an originally 1 per cent. peptone bouillon. A careful analysis of the conditions brought to light certain

[1] Berliner klin. Wochenschrift, 1894, No. 30.
[2] Centralblatt f. Bakteriologie, 1896, xix. p. 137.

quite important facts. I had always prepared bouillon by adding to the meat juice, peptone, salt, and alkali before boiling and filtering. This was Koch's original method and is quoted by Abbott in his text-book. Petri and Maassen,[1] on the other hand, have more recently recommended the boiling and filtering of the meat-juice before the accessory ingredients are added. This method is in vogue in many laboratories. Suffice it to say that by adding the peptone to the meat-juice before boiling and filtering much of that ingredient of the peptone available for the production of toxin is lost. This observation was confirmed in several series of experiments, the details of which would occupy too much space. I varied the time of adding the peptone and the alkali, as well as the quantity of peptone from flask to flask, keeping the other conditions the same. The result was in all cases in favor of adding the peptone *after* the preliminary boiling and filtering. A little less toxin was found when the meat-juice was first made alkaline. At any rate this is not to be recommended, as the coloring-matter is dissolved by the alkali and gives the bouillon a dark color.

The peptone thus loses something which is precipitated out in combination with the albuminous and other substances in the muscle. It has also appeared probable, although I do not wish to state this positively, that still better results are obtained if the peptone is added in sterile solution, with little or no subsequent heating. This, however, is hazardous and not necessary. The mutual action of the peptone and meat-juice is noticeable during the process of boiling for a minute before titration. With the peptone a prompt precipitation occurs, which forms as a scum and leaves the fluid clear. When peptone is absent, more prolonged boiling does not cause clarification, and this appears only after the alkali has been added and the boiling continued. I am inclined to believe that these observations will explain the failure of some to produce a concentrated toxin. It does not, however, account for the whole difficulty, as much of this is dependent on the presence of muscle sugar.

The variation in the amount of toxin accumulated in presence of the same quantity of peptone and of varying quantities of peptone is thus dependent on the preparation of the bouillon and the quantity of

[1] Arbeiten a. d. Kaiserl. Gesundheitsamt, 1892, viii. p. 311.

muscle sugar. In my own work 1 per cent. peptone added after the boiling and filtering of the beef-juice when the latter was nearly free from muscle sugar, yielded in eight days as strong or stronger toxin than a 2 per cent. solution. When the muscle sugar appeared in appreciable quantity 2 per cent. was necessary. More than this I have not used. A definite explanation of these puzzling phenomena is not at present within reach. A theory which seems to account for them very well I have formulated, but owing to the want of time I have not been able to carry out the many experiments necessary to demonstrate it. It is in brief as follows:

The toxin produced by diphtheria bacilli is an intermediate product of metabolism derived from the peptone and subsequently consumed by the bacilli. It is produced only in the membrane in contact with oxygen. When the acidity of the bouillon is very low a rapid surface-growth appears, the alkalinity soon reaches to and beyond the phenolphthalein point, the growth ceases, and the toxin is secure. When the presence of muscle sugar produces a decided but not inhibitory increase in acidity, a high initial alkalinity starts the membrane, and produces some toxin which may be detected in the early days, as Park has shown. The growth is now partly checked and largely subsides. In this stage toxin is not formed, but probably used up by the bacilli in the oxygen-free depths of the liquid, thereby keeping up their growth until a less acid state is reached, which again brings the growth to the surface. The larger quantity of peptone is now needed to make new toxin and carry the growth along to a still more alkaline condition. If enough peptone has been added originally and the bacilli have not been too much depressed by the great range of reaction, some toxin will still be formed and finally appear after three or four weeks.

This theory accounts, I think, for all the phenomena observed, and I have numerous isolated illustrations to which it is readily applicable. It accounts for the disappearance as well as the reappearance of the toxin so puzzlingly variable in practice. At first I thought that the acid formed combined with the toxin to make it inert. This easy way out of the difficulty was shown to be not probable by a simple experiment.

Toxin filtered and containing 0.2 per cent. carbolic acid received as much lactic acid as was necessary to make the acidity 3.6 per cent., at which point toxin is not detected in cultures. The acid toxin was

placed in the incubator to approximate the environment of the cultures, and tested on guinea-pigs from time to time. After several weeks the test showed no decline in toxic power and the experiment was abandoned. On the other hand, Roux and Yersin state that acids neutralize the toxicity of cultures and alkalies partially restore it. The amount of acid necessary is not stated. My theory stands in opposition to that of Roux and Yersin, who regard the diphtheria toxin as an enzyme, as well as to the most recent utterances of Brieger and Boer, who maintain that the toxins of diphtheria and tetanus do not possess any of the characters of peptone, albumose, or albuminate.[1] Nevertheless, the fact that this great body of workers have overlooked for years those simple conditions which control the accumulation of diphtheria toxin in bouillon warns us not to regard too promptly their theories as well-attested articles of scientific commerce.

MISCELLANEOUS OBSERVATIONS.

The effect of the diphtheria toxin upon the guinea-pig is worthy of a few remarks, as the action of the poison is only second to that of its antidote in interest. The action in general reminds one of the behavior of some septicæmic bacteria having different degrees of virulence. The strongest toxin, which proved fatal in doses of 0.03 to 0.04 c.c. within twenty-four hours, gave no visible evidence of its power. Even a local reaction was wanting. For this reason after the first tests with this very concentrated poison I was inclined to doubt that the cause of death was the toxin injected. With toxin somewhat weaker local hemorrhagic disturbances are pronounced. With that still weaker the hemorrhages give way in part to subcutaneous œdema. The lungs, when death ensued during the second and third day, were, as a rule, in a state of œdema. The pleural cavity contained much clear serum, and the sodden, hyperæmic lung tissue assumed in spots a red flesh color. When death ensued later than the third day the lungs were normally collapsed. Locally, sloughing took place in many cases, probably as a result of vascular disturbances. The paralyses reported by some observers I have never seen, although guinea-pigs have been kept in all cases after recovery for some time and used either for breeding or in other lines of work.

[1] Uber Toxine und Antitoxine. Zeitschrift f. Hygiene, 1896, xxi. p. 259.

Several times paralysis was feigned by a cicatricial contraction of the skin over the site of the inoculation. A certain number became emaciated some time after full recovery. They grew literally smaller and moved about the pen with arched back. The bones could be felt through the skin. In all such cases after they had been chloroformed the kidneys were found remarkably pale and in some instances perhaps a little enlarged. I do not believe that this condition is due to the toxin, or the serum and toxin, as the case may be, but that it is peculiar to, or at any rate not uncommon, in the guinea-pig living in confinement, as the disease was found in both young and old untreated guinea-pigs.

The large amount of labor which has been expended in comparing the virulence of diphtheria bacilli from different sources is all but wasted. Cultures in beef broth from different sources, and even with relatively large amounts of dextrose added, have been used for this purpose. In order to compare accurately the toxin-producing power of diphtheria bacilli, we must first offer them the best conditions possible. Bacilli which ordinarily yield little or no toxin, may produce a strong toxin in glucose-free bouillon. The necessary conditions for comparative tests are: 1. Bouillon nearly free from muscle sugar, and, if possible, use of the same bouillon for all comparative tests. 2. A precise knowledge of the amount of acidity still likely to be formed and of the initial acidity of the bouillon, in order that if the same bouillon be not at hand other bouillon like it may be furnished. 3. The same kind of peptone. 4. The same surface-exposure relative to the bulk of the liquid. The layer of fluid should not be deeper than 2 to 3 cm. 5. The same period of growth for all cultures. 6. The injection of a preferably filtered fluid diluted to 1 c.c. with sterile water.

The terms virulence and toxicity have been carefully held apart by some writers, although it does not appear that virulence is anything more than the capacity to produce toxin. The diphtheria bacillus itself, restricted as it is to the mucous membrane, does not play any recognizable part in the disease. In the subcutaneous tissue of inoculated guinea-pigs I have been unable to note any multiplication, but rather a rapid disappearance of the injected bacilli. If virulence has any meaning beyond that of producing toxin, it must be that in bouillon the toxin produced may be different from that produced in

the subcutis of guinea-pigs from the fluids there present. Park has also shown that diphtheria bacilli freed from the culture fluid are practically inert in the subcutis of guinea-pigs.

The toxin-forming capacity of various substances, such as albumin, albumoses, varieties of peptones, serous exudates, etc., may be readily determined by adding them to bouillon containing only traces of muscle sugar and no peptone. Since the simple bouillon produces very little toxin, its effect can be eliminated without difficulty in a control culture.

The question of pseudo-diphtheria bacilli, which has received so much attention and which seems to have tapered down to the production or non-production of acids, is also likely to reach a more satisfactory solution in view of the more definite knowledge we now possess. An extended experience in testing the acid-producing function of bacteria leads me to state that if, as has been claimed, the pseudo-diphtheria bacilli do not act upon dextrose, there exists a most profound difference between these and the true diphtheria bacilli, sufficient to separate them for once and all. To determine, however, that such a difference exists, we must be certain that dextrose is actually present in the fluid employed, from which acids may be produced. In all cases it is best to add 1 per cent. dextrose to the bouillon. If this remains alkaline, any acid-producing function may be safely regarded as lacking in the bouillon under examination.

I have frequently noticed that in contaminated cultures the toxin has not been injured to an appreciable degree. Such cultures are often far beyond the companion flasks toward alkalinity, and adventitious bacteria have been frequently anticipated in titrations by reason of a greater alkalinity of the culture. The question is an interesting one as throwing some light on the reported increase in virulence of bacteria in mixed cultures. Possibly the greater alkali-producers hurry over the acid period and pave the way for a stronger toxin of the pathogenic bacteria, which are, as a rule, the weaker alkali-producers—a fact easily noted in the fermentation tube. The study of such invasive bacteria as hog-cholera bacilli in mixed cultures has led me to expect only permanent harm to one or both species when growing together.[1] A temporary gain may indeed accrue to the toxin-producing forms and

[1] TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, 1894, vol. ix. p. 85.

thus account for some phenomena of symbiosis not otherwise intelligible.

CONCLUSIONS.

1. In ordinary peptone bouillon, the best means of obtaining a concentrated toxin from diphtheria bacilli is first to eliminate the muscle glucose, preferably by allowing the beef partly to decompose. To begin with a low initial acidity without removing the dextrose beforehand, as recommended by Park, has not proved successful in my hands. It is probable that he has worked with beef containing traces of dextrose only. When the total acidity of the bouillon (including initial acidity) in fermentation cultures of *B. coli* does not rise above 1.5 per cent., a very strong toxin may be expected within eight days. To begin with a low initial acidity does not relieve the diphtheria bacilli from the necessity of entering the acid stage to remove the muscle sugar, which process is eventually inimical to the toxin. A low initial acidity is, however, of advantage in most cases after the muscle sugar has been nearly eliminated. I would suggest as a standard 1 per cent. acidity (which would mean that 10 c.c. of normal alkali per litre of bouillon is necessary to produce a faint-pink coloration with phenolphthalein). Another point secondary in importance only to the muscle sugar is the addition of peptone after the beef-juice has been boiled and filtered. With sugar-free beef 1 per cent. Witte peptone added as stated will furnish as strong a toxin as 2 per cent. peptone. The second precipitate formed when the peptone is added may or may not be filtered out. Its removal does not affect the production of toxin. The change undergone by the peptone in the meat-juice, the writer hopes to investigate in the near future.

The above suggestions, epitomized, mean that it is necessary to prevent a too great amplitude of the reaction-curve, which, besides manifestly consuming the toxin, has a depressing effect on the growth of the diphtheria bacilli. The whole reaction-curve is pushed upward toward the phenolphthalein neutral line and lies wholly above the 2 per cent. acid line, or, better still, above the 1.5 per cent. line. The entire period of growth is thus neutral or alkaline to litmus, and very much shortened, since the alkaline limit is soon reached. (Curve B, Chart III.) The toxicity of the bouillon cultures under these con-

ditions is from 10 to 20 times greater than that of the cultures prepared in the usual way.

2. A working hypothesis which interprets the variable phenomena of toxin production very satisfactorily assumes the toxin to be an intermediate product of metabolism of the diphtheria bacillus consumed in the course of growth. When the life of the culture is long-drawn out by the presence of muscle sugar the toxin is formed slowly and in part disappears, but may be made to reappear by adding more peptone. When the life of the culture is made short by keeping it alkaline and favoring aërobic growth much toxin is produced, and but little consumed. This hypothesis, which I hope to subject to more direct, rigorous examination, places all phenomena on a strictly biological basis and makes oxygen, acids, etc., act upon the bacteria by favoring or inhibiting their activity, and not upon their products.

3. The virulence and toxicity of diphtheria cultures are probably identical and should signify the toxin-producing power of diphtheria bacilli under generally accepted standard conditions most favorable to the bacilli.

4. The occasionally reported increase in virulence of bacteria in mixed cultures may be due solely to a change in the reaction of the culture fluid by one bacterium which becomes favorable to the toxin-producing power of the other.

SUPPLEMENTARY DESCRIPTION OF CHARTS.

The curves are constructed by connecting the dots which represent the result of the titration of culture fluid, at the time designated in the horizontal column of figures above, with $\frac{N}{20}$ NaHO and phenophthalein. The vertical line of figures on the left indicates the amount of normal alkali consumed per hundred cubic centimetres of culture fluid. In every case 5 c.c. of the culture fluid were mixed with 45 c.c. distilled water, brought to a vigorous ebullition in a porcelain evaporator to eliminate CO_2 and $(NH_4)_2CO_3$, and the $\frac{N}{20}$ alkali added while the fluid was hot.

Chart I. This explains itself. See also remarks in the text. The fall in the curve of the control culture indicates relatively the small amount of muscle sugar present in the fresh-beef bouillon used. Attention is again called to the absence of any power of the diphtheria bacillus to act upon lactose and saccharose.

Chart II. For the main facts relating to these curves, see text. The fall in curve of flask 1 indicates only a small amount of muscle sugar. The rapid disappearance (oxidation) of the acids formed is shown by the acute downward loops of the curves. The low initial acidity which enabled the bacilli to multiply abundantly before the strongly acid period was reached, and to form promptly a vigorous membrane, accounts for the rapid recoil. Those portions of the upward curves which are nearly horizontal for a short distance are probably due to disturbance of the surface membrane caused by handdling the flasks. The short period of acidity would lead us to expect a marked accumulation of toxin. This was actually the case. On the fifteenth day flasks 2, 6, and 8 were placed in the cold and the filtrate tested on guinea-pigs in a preliminary way: Flask 2, 0.05 c.c. fatal to 250-gram pig in eighteen hours; flask 6, eighteen hours; flask 8, twenty-eight hours. The depressing effect of the dextrose upon the toxin is thus shown in flask 8, which had received the largest quantity of dextrose (0.17 per cent.). The whole series, however, produced a large amount of toxin, for the combined filtrates of all flasks resulted in a fluid of which 0.02 c.c. was fatal to a 280-gram pig in thirty-six hours.

Chart III. Curves of bouillon made from fresh beef (A, C) and from decomposed beef (B).

A. Curves designed to show the effect of varying the surface exposure upon the reaction-curve, thus: In flask 1 there was about one square cm. of surface to 16 c.c. of fluid; in flask 2, 20 c.c.; in flask 5, 3.4 c.c.; in flask 6, 3 c.c.; in flask 7, 2 c.c. Flasks 3, 4, and 8 became infected in the course of the work. The removal of 5 c.c. of fluid for titration from time to time increased the surface area somewhat, relatively more for 1 and 2 than for the other flasks. In all flasks a feeble membrane appeared at the start, then largely subsided. Later on a second quite vigorous membrane appeared as the curve ascended. The toxicity of 2 and 6 was tested on the twentieth day. Of flask 2, 0.1 c.c. produced a slough in a 350-gram pig; of flask 6, 0.1 c.c. produced death in a 435-gram pig in six days. The curves and the toxin tests illustrate the depressing effect of a too small surface exposure when much acid has to be disposed of. The feebleness of the toxicity in this bouillon is also due to the fact that the peptone was added to the beef infusion before boiling.

CHART I.

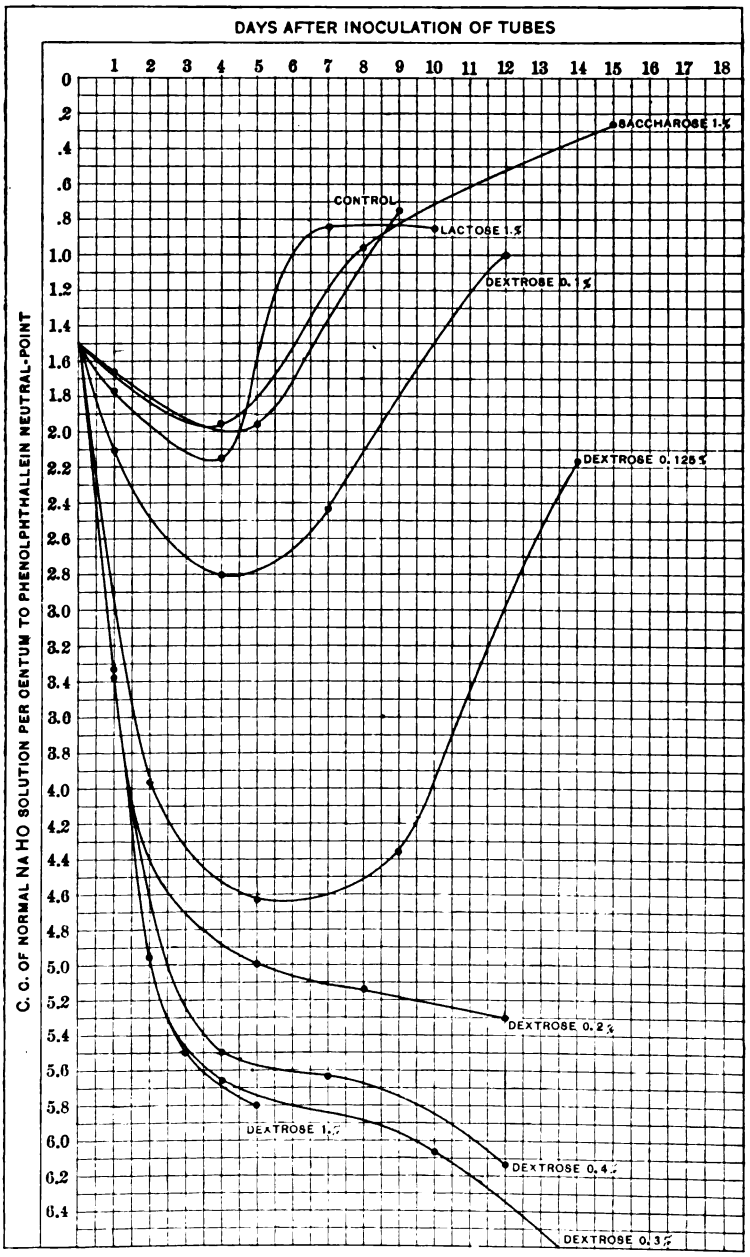
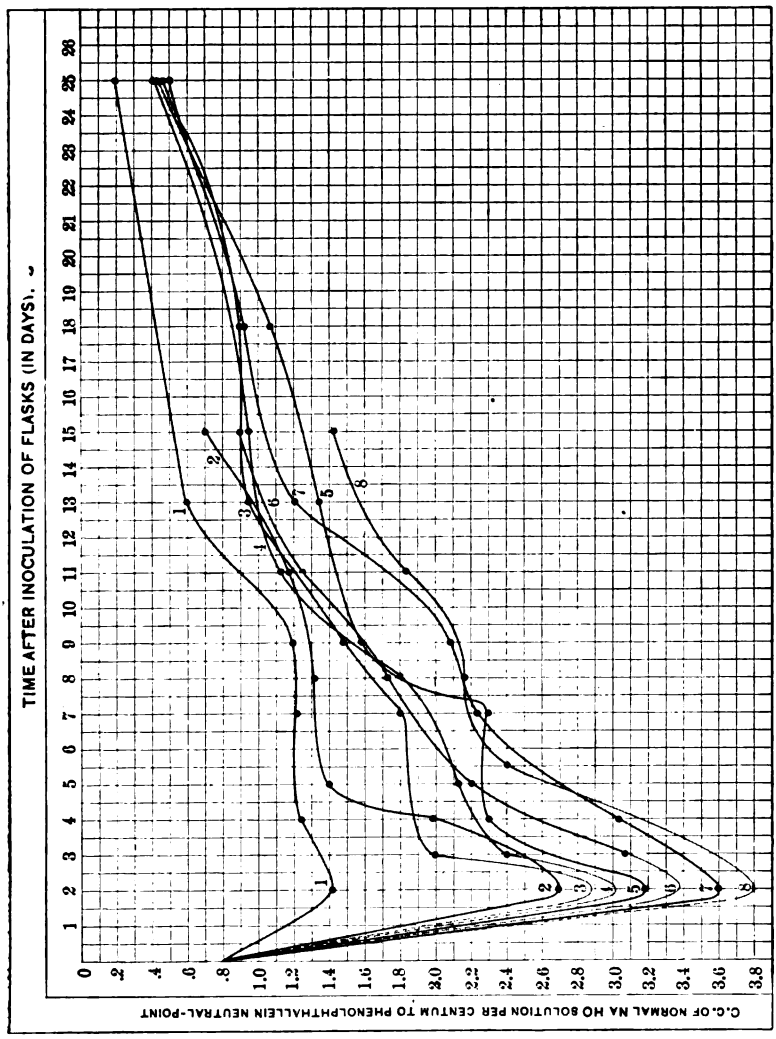
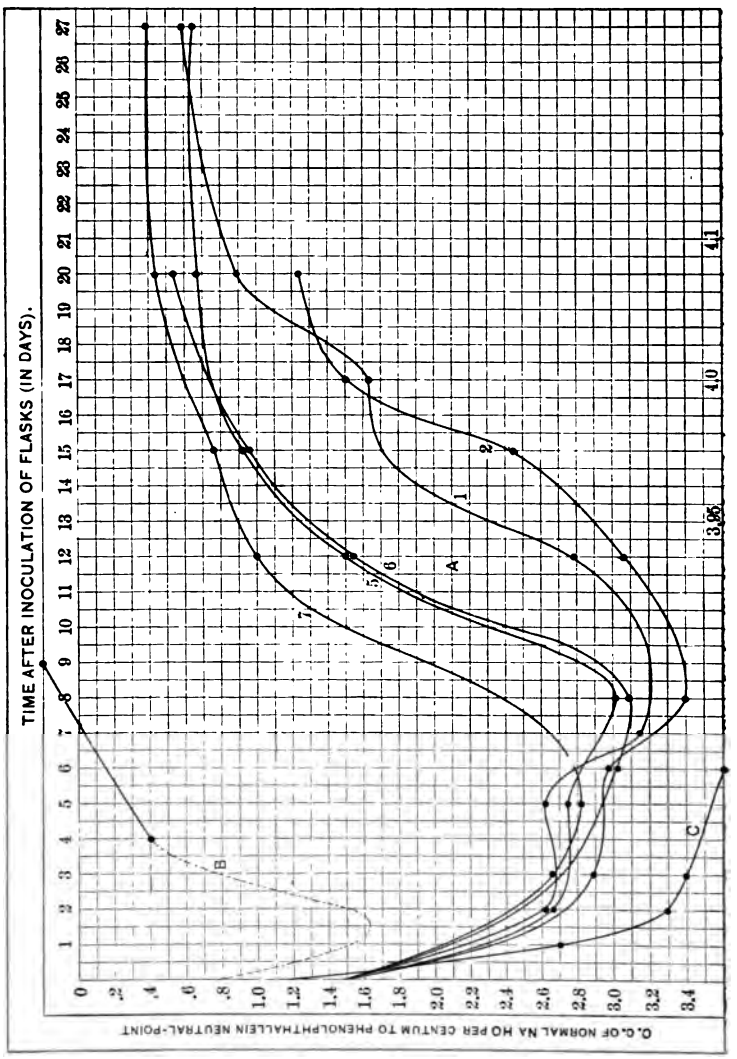

DAYS AFTER INOCULATION OF TUBES
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
0 .2 .4 .6 .8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6 2.8 3.0 3.2 3.4 3.6 3.8 4.0 4.2 4.4 4.6 4.8 5.0 5.2 5.4 5.6 5.8 6.0 6.2 6.4
C. C. OF NORMAL NA HO SOLUTION PER OENTUM TO PHENOLPHTHALLEIN NEUTRAL-POINT
SACCHAROSE 1.%
CONTROL
LACTOSE 1.%
DEXTROSE 0.1%
DEXTROSE 0.125%
DEXTROSE 0.2%
DEXTROSE 1.%
DEXTROSE 0.4%
DEXTROSE 0.3%

CHART II.


TIME AFTER INOCULATION OF FLASKS (IN DAYS).
C.C. OF NORMAL NA HO SOLUTION PER CENTUM TO PHENOLPHTHALLEIN NEUTRAL-POINT

B. This curve is that of a two-per-cent.-peptone bouillon from decomposed beef. The peptone was added to the filtered broth. The rapid trend of the curve toward and beyond the phenolphthalein zero-point is a sure indication that much toxin will be found. On the ninth day 0.05 c.c. of the filtrate was fatal to a 325-gram pig in thirty to thirty-two hours.

CHART III.



C. Curve tending toward extreme acidity, as shown by the rapid descent and the figures along the lower margin of the chart. Bouillon producing this curve, so disastrous to the accumulation of toxin, is frequently encountered during the warm season from April to October.

DISCUSSION.

DR. ERNST: I would like to ask Dr. Smith how he prepares his beef for partial putrefaction; does he chop it up first?

DR. THEOBALD SMITH: I leave it pretty nearly in mass.

DR. B. M. BOLTON: We are very much indebted to Dr. Smith for having first pointed out that the development of the toxin in the cultures is largely influenced by the presence or absence of the muscle sugars. This discovery has enabled us to produce the toxin without any difficulty.

My practice now is to have the beef chopped up fine and allow it to stand a day or so until it becomes somewhat offensive, and in this way I am now able to get toxin of very great strength.

I would like to ask Dr. Smith whether he has tried the use of yeast in eliminating the sugar? I have tried a ferment of that kind with some success.

DIPHTHERIA ANTITOXIN SOMETIMES FOUND IN THE BLOOD OF HORSES THAT HAVE NOT BEEN INJECTED WITH TOXIN.

By B. MEADE BOLTON, M.D.,
OF PHILADELPHIA.

Everyone who has undertaken the production of diphtheria antitoxin has encountered a marked difference in the behavior of the horses undergoing inoculation. With some horses it is a matter of very little difficulty to obtain antitoxin of high potency in a comparatively short time. With others it seems impossible in any way to obtain strong antitoxin, and with others again there is such a violent reaction, even with small doses of toxin, that it is impossible to continue inoculation. It occurred to me that the explanation of this might be found in the normal differences of the blood in the different animals. In order to test this, all the horses that were afterward used for the production of antitoxin for the city laboratory were first tested as to the presence of antitoxin normally. It was, perhaps, to be expected that marked differences in this respect would be observable. I had rather expected, if there were any differences, that these would be gradual, that all horses might exhibit more or less antitoxic power in their blood. But from the results of the tests I am inclined to believe that this is not the case. There is in some cases a notable amount of antitoxin, in others it seems to be totally lacking. It seems to be present to a certain definite extent, or to be entirely absent.

In all the blood-serum of twelve healthy horses was tested previous to injection with diphtheria toxin. Out of this number three were found to possess antitoxin of such strength that 3 c.c. of the serum were capable of neutralizing ten times the minimum fatal dose for guinea-pigs—*i. e.*, $\frac{1}{30}$ of a normal antitoxin unit. In all three horses

the strength of the antitoxin seemed to be the same. The guinea-pigs injected with 3 c.c. all remained alive and well, those injected with a less amount all succumbed promptly to the accompanying dose of toxin. Injections of blood-serum from horses not possessing normal antitoxin exerted no influence even in larger doses up to 5 c.c. The difference seems to be clearly one of quality and not of quantity, an essential difference in some constituent of the blood.

The behavior of the horses possessing antitoxin normally in their blood presents certain points of interest on injections of toxin. These horses show much less reaction at the start than other horses, and it is possible to increase the doses to a certain point much more rapidly without causing alarming symptoms. After the dose has been increased till it reaches about 100 c.c. or more the reaction seems to be as marked as in those horses that have had to be brought up to this dose more gradually. Two horses with antitoxin in their blood normally and two without were started together. One of the latter reacted so strongly that it was impossible to continue even with very small doses. The other three horses have been continued. Up to the present time one of the horses, with antitoxin normally present, has received nearly 3 litres of toxin, the other over 4 litres,[1] and the horse without the antitoxin normally present has received less than 2 litres, and yet they all show about the same amount of reaction at present from injections of 100 c.c. of toxin. At the start, where the doses were small, there was practically no reaction in the horses in which the antitoxin was present normally, whereas in the other horse there was always decided reaction.

One of the horses with antitoxin normally present, the horse that has received about 3 litres of toxin, is beginning to furnish strong antitoxin, almost 1000 units to 10 c.c. The other horse with antitoxin normally present, the horse that has received over 4 litres, furnishes very weak antitoxin, less than 600 units to 10 cc. The horse that had no antitoxin normally, that had received nearly 2 litres of toxin, furnishes quite strong antitoxin, almost 1000 units to 10 c.c. It would seem from this that the presence or absence of more or less antitoxin normally has no effect upon the ultimate production of artificial antitoxin by inoculation, but when present enables the inoculations to be made with less risk to the animal.

[1] This animal has since died.

It is difficult to explain the presence of antitoxin normally in the blood of horses. Wassermann[1] found antitoxin in the blood of healthy persons, who claimed never to have had diphtheria, but he inclined to the belief that these persons at some period must have suffered from unrecognized diphtheria. Orlowski[2] also found diphtheria antitoxin in the blood of children who had presumably never suffered from diphtheria, and he also found it in the blood of convalescents, as others had done. Orlowski does not accept Wassermann's explanation, because he does not find that the age of the children has anything to do with the presence of normal antitoxin, and, moreover, he finds that the antitoxin present after convalescence disappears.

DISCUSSION.

DR. FLEXNER: This interesting observation of Dr. Bolton upon the antitoxic substances contained in the normal heart-blood is confirmed anew in the experiments of Fisch and v. Wunschhein, to which I alluded a moment ago, these investigators having found that 85 per cent. of the blood-serums obtained at childbirth possessed antitoxic power for the diphtheria infections in guinea-pigs. Pfeiffer and Kalle have also shown that the blood-serum of normal goats is capable of influencing the intraperitoneal cholera infection in guinea-pigs. The effect of the introduction of such normal blood-serum is to call forth, first, a destructive (bactericidal) effect upon the introduced cholera bacilli; but since the dead bacilli are more toxic than the living ones, further influence is exerted by the serum in provoking the development of antitoxic substances to overcome the liberated toxins. We have reason to believe that the antitoxins in general do not act simply by a chemical neutralization of the toxins, but that indirectly they provoke through cell stimulation the formation of the true neutralizing principle. And a similar property would appear to be exerted by the normal goat's blood in preventing cholera intoxication in the guinea-pig.

DR. THEOBALD SMITH: I have no doubt that those persons who have charge of the making of antitoxin will be glad to hear of Dr. Bolton's experiment, from the fact that there are some horses that will not produce antitoxin beyond a certain strength, and that the quantity of toxin injected has

[1] Wassermann: Die Immunität Gesunder gegenüber Diphtherie. Deutsche med. Wochenschr., 1894.

[2] Orlowski: Ueber die antitoxischen Eigenschaften des Blutserums bei Kindern. Deutsche med. Wochenschrift, 1895.

no direct relation to the amount of antitoxin produced. I hope that Dr. Bolton will continue this line of work.

DR. JACOBI: I would like to ask if the age of the horse has anything to do with it? I ask this because recently I have seen the statement that the blood of the newly-born is rather more germicidal than the blood of older individuals.

DR. BOLTON: I cannot say anything about the age, because upon the horses that were furnished to me the age could not be determined.

I think if Dr. Flexner will look at the paper referred to again, he will find that it deals with germicidal properties in the blood of these animals.[1]

DR. FLEXNER: I accept that statement.

[1] In Pfeiffer's article, "Ein neues Grundsetz der Immunität" (Deutsch. med. Wochenschr., 1896, No. 8), Pfeiffer states that there is a certain amount of cholera antitoxin normally present in the blood of goats, and that inoculation with dead cultures does not increase this. This statement had escaped my memory.

THE PRODUCTION OF ANTITOXIN BY THE PASSAGE OF ELECTRICITY THROUGH DIPHTHERIA CULTURES.

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AND

HERBERT D. PEASE, M.D.,
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Prochownik and Späth, in 1890, made the observation that bacteria adhering to the positive pole of an electrical current are retarded in growth or killed, according to the strength and duration of the current. In these experiments results were obtained only by growing the bacteria in agar on the electrodes themselves, and then dipping these in salt solution and passing the current. Simply passing the current through a liquid culture or suspension of the bacteria had no effect. They attribute the effect to the chlorine gas liberated at the positive pole.

Apostoli and Laquerrirèe found that passing a current through bouillon cultures had the effect of killing bacteria if the poles are placed close together. The action is independent of the heat that is produced, and takes place only at the positive pole. The action is believed to be due to the decomposition of the nutrient solution into acids and to the liberation of oxygen. The electricity itself is not believed to play any part directly.

Forth found that electrical currents lessen the fermentative power of yeast cells. He concludes that the action is due to the products of electrical decomposition, notably to the development of ozone.

Tolomei found that only strong discharges from a Ruhmkorff apparatus, placed very close over the surface of the liquid, stop acetic-acid fermentation. These discharges do not cause a sterilization of the liquid, and fermentation begins again slowly after the discharge.

Spilker and Gottstein tested the effect of electricity upon cultures and suspensions of bacteria in various fluids. The bacteria were destroyed in suspensions in water and in "weiss Bier," but not in milk. The suspensions in blood were sterilized by the electrical current, and it was supposed that the iron in the blood had something to do with the action; but suspensions in solutions of various salts of iron were not sterilized by the electrical current. Suspensions in solutions of iron albuminate were retarded in growth, but development of bacteria recommenced after eight days.

Verhoogen found that there was a destruction of bacteria around the positive pole with weak currents, but if the current is made strong enough there is this action also around the negative pole.

Charrin reported some observations of Gautier made on suspension of bacillus pyocyaneus in solutions of iodide of potassium and in artificial serum. The positive electrode consisted of copper and was dipped into the suspensions of the bacteria. In both cases the bacillus was deprived of its power of producing any color when grown on agar after the current was passed for seven minutes; longer action was found to retard subsequent growth and even to cause sterilization.

Krüger found that the constant current is able to suspend growth but not to kill bacteria where all chemical action due to the products of decomposition of the nutrient material is excluded. Cultures subjected to certain strength of current for a certain length of time possess immunizing properties.

Smirnow inoculated a large number of rabbits with 0.5–0.7 c.c. of a bouillon culture of diphtheria two or three days old, and twenty-four hours afterward when the animals were very sick he injected 8 to 10 c.c. of the product from the positive pole of electrolyzed toxin. The animals all recovered. In order to convert 200 c.c. of toxin into antitoxin he finds it necessary to use a current of 80 milliampères for not less than sixteen to eighteen hours. The action of the current on the toxin is apparent at the positive pole by a bleaching of the bouillon, at the negative pole by a darkening of the bouillon. In applying the current Smirnow used a U-shaped tube with a glass stopcock in the middle.

Krüger finds that the calibre of the U-tube used to contain the culture should not be more than 18 mm., and that the entire length should not be more than 22 cm. The current should be made to pass

upward through the liquid. Krüger, moreover, obtained the best results by scraping the diphtheria bacilli off of agar cultures and making a suspension in 1 per cent. salt solution. This he finds better than bouillon cultures. He was able to prevent death in rabbits inoculated with virulent cultures by injection of 3 c.c. of kathod product, and he found he could save rabbits with 2 c.c. of the crude product.

Smirnow finds that diphtheria antitoxin, which cures inoculated rabbits and guinea-pigs even in advanced stages of sickness, can be obtained by electrolysis; that the strength of the antitoxin depends largely upon the strength of the toxin that has been subjected to the current. Moreover, that it depends upon the degree of acidity of the liquid at the negative pole. This acidity should be such that 0.9 to 1.3 c.c. of normal soda solution neutralizes 1 c.c. of the electrolyzed product. This degree of acidity is the optimum for guinea-pigs, but for rabbits the current must be allowed to act for a longer time and the acidity should be such that 1.5 to 1.7 normal soda solution is required to neutralize it. He finds that any of the electrolyzed product above that which is just sufficient is injurious.

D'Arsonval and Charrin find that continued or intermittent currents of high potentiality attenuate toxins as well at the positive as at the negative pole. They find that toxin treated with a continuous current is simply destroyed by the chemical products of electrolysis and possesses little or no antitoxic properties. But toxin treated with an intermittent current, where the current was reversed about 200,000 times a second, produced quite strong antitoxin in a quarter of an hour. They conclude that the production of antitoxin by an electrical current is due to a violent vibration of the molecules, resulting in a rearrangement, and not to any chemical decomposition.

In the following tests we employed a current from the Edison electric light, which usually has a strength of 110 volts; this was reduced and controlled by a simple rheostat inserted in the current. The apparatus used to hold the liquid cultures consisted of two test tubes connected about the middle by a tube with a stopcock. In some cases the stopcock was of glass, in others of hard rubber. The resulting shape of the apparatus is that of the capital letter H, the vertical arms open at the top and closed below with a platinum-wire electrode melted in. In order to expose a large surface, the wire projects inside the tubes several inches and is coiled up. The cross

arm of the H carries the stopcock. Following Krüger's suggestion, the length of the lower half of the vertical arms and the transverse connection together were made to measure 22 cm., and the diameter 19 mm. The apparatus with these dimensions gave better results than a larger apparatus made after a similar pattern with a hard-rubber stopcock. In all cases the current was made to pass upward through the liquid. The strength of the current was determined with a Weston milliampèremeter.

The action of the current is made evident by the evolution of gas bubbles, which are given off from the electrodes and rise and form a foam at the top. A precipitate quickly forms in both tubes, but more abundantly over the positive pole, and the liquid in this tube also becomes lighter in color. After the stopcock is turned off, cutting off the current, the precipitate soon settles to the bottom. The fluid over the negative pole becomes darker in color. There is a peculiar odor given off resembling that of chloride of lime, but it was found that the fluid contained only one-tenth of one per cent. of chlorine. The strength of the current increases gradually as it is allowed to pass, and has to be regulated with the rheostat from time to time.

Tests were made on bouillon cultures grown for varying lengths of time in the incubators; some of them filtered through several thicknesses of filter paper and some of them unfiltered. The current usually employed varied from 44 to 72 milliampères, and was allowed to act, as a rule, for two hours, though some tests were made with cultures that had been subjected to the current for longer and shorter periods than this. In all cases the strength of the cultures was tested on guinea-pigs previous to the passage of the current. The tests as to whether antitoxic property was developed by electrolysis were made by Behring's method, *i. e.*, by administering ten times a certainly fatal dose of diphtheria-toxin along with varying amounts of the electrolyzed products, either mixed with the toxin or injected at a different place in the animal.

These tests soon showed that there is a production of antitoxin over the positive pole, as the following result of one of several experiments will show:

A guinea-pig, weighing 230 gms., was inoculated under the skin with a mixture of 1 c.c. of diphtheria-toxin and 5 c.c. of the product from the positive pole. A similar guinea-pig was inoculated at the

same time with 1 c.c. of the same toxin mixed with 5 c.c. of the product of the negative pole. Before the current was passed the toxin was found to be of such strength that $\frac{3}{10}$ c.c. would kill an average-sized guinea-pig in forty-eight hours. The toxin used to mix with it after electrolysis killed in doses of $\frac{1}{10}$ c.c. in forty-eight hours. The guinea-pig inoculated with the mixture containing the product from the positive pole remained alive and showed no symptoms of disease. The other animal died promptly in forty-eight hours. Two and a half cubic centimetres of the electrolyzed toxin were insufficient to neutralize ten times the minimum fatal dose of toxin. In order to test whether the product of the negative pole was in itself poisonous, a guinea-pig was injected with 5 c.c. of it and remained perfectly well, so the toxin properties are destroyed at the negative pole, but no antitoxin is developed.

The strongest antitoxin we were able to obtain was such that 2 c.c. neutralized ten times the minimum fatal dose for guinea-pigs. In a single experiment made on rabbits by intravenous injection, neither 2 c.c. of the product of the negative pole nor 3 c.c. of the positive pole counteracted 6 c.c. and 5 c.c. respectively of toxin.

It occurred to us to try whether the presence of the bacilli themselves would influence the result. So unfiltered cultures and the sediment in old bouillon cultures were tried, but the result was the same, viz., 2 c.c. of the product from the positive pole counteracted ten times the minimum fatal dose, while the same amount from the negative pole had no effect.

Tests with a much weaker current for a somewhat longer time seem to indicate that this is an advantage. But if the current, even though very weak, be kept up too long—*e. g.*, a week or more—the antitoxin seems to be less potent.

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Smirnow: Ueber die Behandlung der Diphtherie mit künstlich dagestellten Antitoxinen. Berl. klin. Wochenschr., 1895, Nos. 30 and 31.

D' Arsonval et Charrin: Compt. rend. de la Société de Biologie, 1896, Nos. 3, 4, and 5.

DISCUSSION.

DR. STERNBERG: Does Dr. Bolton anticipate that it may be practicable to produce antitoxin in this way rather than by the inoculation of horses?

DR. THEOBALD SMITH: I would ask Dr. Bolton if he found, in accordance with the experience of Smirnow, that an overdose of the antitoxin is likely to be injurious to the animal?

DR. VAUGHAN: Smirnow found that if he gave an overdose his animal died of diphtheria-poisoning. It seems to me that his work proved only that he had reduced the virulence of the toxin with the electrical current.

DR. BOLTON: I do not know that it will be of any practical value. The efforts that we have made to concentrate this antitoxin have not been very successful, although we have not made enough experiments to be sure. The strongest antitoxin that has as yet been obtained in this way could not be used because of the bulk.

In regard to the overdose, I have never seen any ill results follow the injection of the material obtained by the action of the electrical current, even when used in large doses. I do not understand Smirnow's results. D'Arsonval and Charrin have recently published a series of interesting experiments, which I did not allude to, but which are alluded to in our paper. They found that the continued use of the intermittent currents of high potentiality attenuated the toxin at the positive as well as at the negative pole. This corresponds with our results. We found that at both poles the toxin was attenuated or even destroyed, and you can inject any amount of the negative or positive product without any injury. They found that toxin treated with the continuous current is simply destroyed by the chemical products of electrolysis and possesses little or no antitoxic power; but toxin treated by the intermittent current produces antitoxin. They consider it due to the violent vibrations of the molecules resulting in a rearrangement of these, and not to any chemical decomposition.

THE TREATMENT OF ANTHRAX IN RABBITS BY THE INTRAVENOUS INJECTION OF YEAST NUCLEINIC ACID.

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AND
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Preliminary Note.

The object of this paper is to report some experiments made along the line indicated in the title. The nucleinic acid was obtained from so-called pure yeast furnished us by the Independent Brewing Co., of Chicago. The method of isolating the nucleinic acid has already been published by us. It is essential that the albuminous and mucin-like bodies should be completely removed. If this be imperfectly done, the intravenous injection causes speedy death. All the injections were made into the external jugular vein. The anthrax bacillus used in these experiments was of full virulence, but the number of germs used in each inoculation was small. Beef-tea cultures of from one to three days' growth were employed. One loop of such a culture was placed in two cubic centimetres of beef-tea, and one-tenth of a cubic centimetre of this was injected under the skin of the back. The time elapsing between the inoculation and the treatment, also other data, is shown in the tables. The solutions of nucleinic acid used were neutral or very feebly acid to litmus paper.

These experiments certainly show that comparatively large quantities of nucleinic acid may be injected into the blood of rabbits without causing death.

The Treatment of Anthrax in Rabbits by the Intravenous Injection of Nucleinic Acid.

Group I.—Animals treated with a 10 per cent. solution of nucleinic acid.

No.	Weight, grams.	No. of c.c. given.	Time of treatment after inoculation.	Result.
1	1502	10	25 hours.	Survived.
2	1090	10	25 "	"
3	720	9	25 "	"
4	1545	18	26 "	"
5	1955	10	23 "	Died after 96 hours.
6	1764	10	23 "	Survived.
7	1380	8	28 "	Died after 96 hours.
8	1824	10	22 "	Survived.
9	1800	15	8 "	"
10	1250	15	8 "	"

Died, 2 = 20 per cent. Survived, 8 = 80 per cent.

Group II.—Animals treated with dilute solutions of nucleinic acid.

No.	Weight, grams.	No. of c.c. given.	Strength of solution.	Time of treatment after inoculation.	Result.
1	1700	60	0.5 per ct.	24 hours.	Survived.
2	1510	75	0.5 "	22 "	"
3	1285	47	0.5 "	24 "	"
4	1650	15	0.2 "	6 "	"
5	1100	15	0.2 "	7 "	"
6	1150	15	0.3 "	8 "	"
7	1355	17	0.3 "	8 "	"
8	1030	20	0.2 "	4 "	Died after 26 hours.
9	1250	20	0.3 "	5 "	" " 56 "
10	1745	25	0.2 "	5 "	" " 60 "
11	1030	17	0.3 "	5 "	" " 40 "
12	2030	25	0 3 "	5 "	Survived.
13	760	7	0.3 "	5 "	Died after 36 hours.
14	980	15	0.3 "	6 "	" " 36 "
15	2120	27	0.3 "	6 "	Survived.

Died, 6 = 40 per cent. Survived, 9 = 60 per cent.

GROUP III.—Untreated animals.

No.	Weight, grams.	Result.
1	1145	Died after 30 hours.
2	1125	Survived.
3	955	Died after 36 hours.
4	2330	Survived.
5	2110	Died after 120 hours.
6	1170	" " 46 "
7	1175	" " 36 "
8	1030	" " 80 "
9	1350	Survived.
10	1420	Died after 50 hours.
11	1000	" " 40 "
12	690	" " 36 "
13	960	" " 36 "
14	1800	" " 40 "
15	1925	" " 38 "

Died, 12 = 80 per cent Survived, 3 = 20 per cent.

DISCUSSION.

DR. THEOBALD SMITH: I would like to ask Dr. Vaughan how long his control animals lived and how soon he treated the others after the inoculation with the anthrax bacillus.

DR. BOLTON: I would like to know why such small doses of anthrax were used, and whether it is not just barely possible that some of the animals did not get any anthrax bacilli at all by the inoculation? The fact that three of the control animals survived inoculation with this very dilute suspension suggests that some of the other animals escaped infection.

DR. MELTZER: I would like to ask Dr. Vaughan if the 1 per cent. solution was in distilled water or saline solution? I understood him to say that 90 c.c. of a 1 per cent. solution was injected.

DR. VAUGHAN: In answer to Dr. Smith's question I will say that the shortest length of time which a control lived was thirty hours and the longest 120 hours. The treatment was commenced in from five to twenty-four hours after inoculation. The shortest period was five hours and the longest period twenty-eight hours.

It is possible that some of the animals failed to get any of the anthrax. Certainly the three that survived did not get much of it.

The solution was a saline solution and was neutral to litmus paper or faintly acid.

Of course this work will have to be gone over. It is simply suggestive.

TWO VARIETIES OF THE TUBERCLE BACILLUS FROM MAMMALS.

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THE assumption that a pathogenic species so-called does not contain within itself a greater or smaller number of varieties with which bacteriology tacitly started out about fifteen years ago has been fairly well demolished up to the present time. Varieties have been found among nearly all of those specific forms which have received a considerable amount of attention. Even the tubercle bacillus has been drawn into the circle of specific forms existing as varieties by the work of Maffucci on tuberculosis in fowls. The sharp distinction between mammalian and avian tuberculosis which was thereupon drawn prevailed for a time until recently matters have become more complicated. Koch's remarkable monograph stands on the ground of the unity of the tubercle bacilli which he obtained from human beings as well as from a variety of mammalia. Few investigations appear to have been made subsequently with cultures directly obtained from a case of spontaneous tuberculosis or from guinea-pigs directly inoculated with tissue from such a case. In the study of tubercle bacilli which had been cultivated for a variable period of time and passed from hand to hand, the element of saprophytic modification entered which has some effect upon the virulence and the cultural and, perhaps, morphological characters of the tubercle bacillus.

The subject, as it has been left by some recent writers, seems to point to the existence of tubercle bacilli of varying virulence which bridge over the original chasm between the avian and the mammalian

cultures and which tend to wipe out the specific difference between these two forms.

W. Kruse[1] gives the history of four cultures: One from Pansini (Naples), isolated from tuberculous sputum after having been passed through a guinea-pig; one from Armanni, isolated in the same manner; one from Sanfelice, isolated from tubercles in the lungs of cattle; and one from Straus, of Paris, whose origin seems to have been not positively known. These four cultures failed to produce more than a local disease in guinea-pigs. In two out of twelve rabbits miliary tuberculosis of the peritoneum was produced after intra-abdominal injection. Fowls were infected quite regularly by intra-peritoneal injections. These cultures are, therefore, regarded by Kruse as belonging to the avian variety.

Pansini[2] isolated tubercle bacilli having the characters of the avian variety from a human being and from cattle after passing the tuberculous products through guinea-pigs. Pansini further finds that avian bacilli may occasionally produce tuberculosis in guinea-pigs, and finally concludes that transition-forms do exist.

Fischel[3] is also inclined to look upon the avian and human tubercle bacilli as not sharply separated. His work does not, however, show that he studied cultures isolated by himself.

Johne and Frothingham[4] have reported what appeared to be a diffuse tuberculous infiltration of the mucous and submucous tissues of the intestines in a cow, quite different in appearance and histological character from the lesions of ordinary bovine tuberculosis. Unfortunately cultures did not succeed and subcutaneous inoculation of guinea-pigs failed to produce even a local lesion. The authors are inclined to look upon the case as an infection with avian bacilli.

From these citations it becomes evident, I think, that more study of the tubercle bacillus is needed. I do not deny that the time spent in such study may be regarded as wasted by those who, as it has been recently epitomized, think that the fruitful discovery of Koch has exhausted itself in staining tubercle bacilli. However academic much of this work may appear from this standpoint it is incumbent upon

[1] Ziegler's Beiträge, 1893, xii. p. 544. [2] Deutsche med. Wochenschrift, 1894, p. 694.
[3] Fortschritte der Medizin, 1892, x. S. 908.
[4] Deutsche Zeitschrift f. Thiermedizin, 1895, xxi. S. 438. The Veterinary Magazine, January, 1896.

us to keep training and pruning the tree of knowledge without looking to the right or the left. I, therefore, have considered it worth while to compare somewhat carefully two original cultures from two mammals, which presented not only a different behavior on blood-serum, but also in which the morphology and pathogenic characters showed certain well-defined divergences. The evidence presented is complete because both cultures were compared from the time they were isolated, and not after an indefinite period of growth on culture media.

That such a comparative study may be, at least, fruitful in raising important questions the concluding portion of this paper will amply show.

I.

The source of one of the cultures was an animal related to the raccoon (*Nasua narica*). In this animal which I saw the day after death, on May 12, 1894, the tuberculosis was apparently of intestinal origin. A gland at the root of the mesentery as large as a goose-egg was converted into a sac filled with a soft, viscid pus. The omentum was extensively studded with small tubercles, but the spleen and kidneys were free from disease. The lungs were permeated uniformly with tubercles evidently of embolic origin. Ulcers were reported as having appeared on the body before it died. The owner of this animal, who had kept it as a pet, had succumbed to tuberculosis some time before. It is highly probable that it had contracted the disease from its master. Dr. Frank Baker, Superintendent of the National Zoölogical Park, at Washington, D. C., who kindly brought the animal to the laboratory, thought that it could not have been infected from meat or milk. It was received by him September 27, 1893, and it died May 11, 1894. During this time several other animals of the same species were exposed to similar conditions, but this was the only one to die of tuberculosis. He also adds that it had been a special household pet, very familiar with its master.

A particle of lung-tissue was removed and kept in a sterile dish in the refrigerator until May 16th, when an opportunity was found to inoculate with it two guinea-pigs by placing small particles under the skin. The further history of these animals is given to illustrate the relative virulence.

May 16, 1894. Nos. 174 and 175 inoculated.

July 26th. No. 174, original weight 180 grams; chloroformed (two and one-third months after inoculation).

Enlargement and caseation of kneefold, axillary and retro-peritoneal glands of inoculated side. Other glands, including cervical, bronchial, and retro-gastric glands, enlarged and firm. Spleen very large, and contains multiple tuberculous foci. Liver large, and shows a small number of necrotic patches and many grayish translucent foci. In lungs many grayish tubercles, some with necrotic centre.

August 29th. No. 175 died to-day (after three and one-half months). In this animal the liver was extensively necrosed, the spleen affection less marked. The lungs were dark red and contained a considerable number of rather large (3–4 mm.) tubercles which are mainly grayish translucent in appearance.

These notes show clearly that the tissue inoculated was much less virulent than is the case with tuberculous matter from cattle. The latter is usually fatal to guinea-pigs weighing 300 to 400 grams in four to six weeks, provided tissue be inoculated in which the disease process is still active.

Cultures were made on blood-serum from tubercles in the lungs, spleen, and liver of No. 174. A month later none had shown signs of life. On September 17th, fifty-three days after the inoculation of the tubes, a lung culture and a spleen culture showed distinct signs of growth in one or more places, and bacilli were found agreeing morphologically and tinctorially with tubercle bacilli. The cultivation of this organism in two parallel series from spleen and lungs presented no special difficulties.

On serum from cattle the growth after the second generation was fairly vigorous. It developed into a thin uniform expansion over the surface of the serum, which assumed the appearance of ground-glass. When the bacilli were massed together with a loop the mass had a distinct straw color. It was neither very dry nor very brittle. When it reached the condensation water it soon covered this with a uniform membrane resembling tissue paper, and even pushed itself some distance above the fluid along the walls of the culture tube. A period of two weeks was usually sufficient for the full development of a culture. When the fifth generation was transferred to serum from the dog a very rich, whitish growth formed within two weeks. In the earlier generations some tubes of serum would fail to favor the multiplication of this bacillus, while other parallel cultures were successful. In those tubes in which the growth remained restricted a discoloration would appear by which the growth became brownish in part. This discoloration is an indication of the death of the bacilli.

Transferred upon distinctly alkaline glycerin agar a rather feeble multiplication took place after the fourth or fifth generation. Multiplication on the surface of glycerin bouillon, at first very slow, became after a few gener-

ations quite vigorous. The membrane formed has a peculiar structure. It is composed of a number of disk-shaped, whitish bodies about 1 to 1.5 millimetres in diameter, each representing a centre of growth. These disks loosely adhere to one another and leave spaces here and there. The entire membrane thus resembles heavy lace in a general way. The rapidity of growth on alkaline glycerin bouillon is shown by the following notes:

December 21, 1894. Flask inoculated by transferring a piece of membrane 4 to 5 mm. across.

January 3, 1895. Membrane now 10 mm. across.

16*th*. Membrane now 35 mm. across.

Later on this "lacework" on bouillon had attached to it very thin papery membranes or expansions from 1 to 2 cm. in diameter.

To test the pathogenic power of the pure culture two guinea-pigs were inoculated on the right side subcutaneously on October 31st, from a serum culture twenty-nine days old (second generation of lung series). Each animal received a quantity of the bacilli which could be held with a small loop.

No. 235, male, weight 570 grams, inoculated October 31.

November 16*th*. A healed scar at seat of inoculation. Subcutaneous infiltration one quarter inch thick over an area three-quarters inch in diameter. Neighboring kneefold glands as large as beans.

December 3*d*. Pig evidently ill; chloroformed. Local ulcer with cheesy base and tubercles around it in subcutis. Axillary, kneefold, and retro-peritoneal glands of same side largely necrotic; glands of opposite side with necrotic foci. Spleen enlarged. All Malpighian bodies prominent. Liver sprinkled with small necrotic spots. Lungs contain many grayish tubercles, some with necrotic centre. Right cephalic lobe collapsed.

No. 236, male, weight 580 grams, inoculated at the same time.

November 26*th*. Found dead. Local cup-shaped ulcer with surrounding tubercles. Right kneefold, axillary, and retro-peritoneal glands partly necrotic. In the corresponding gland of opposite side minute necrotic foci. Spleen enlarged to twice normal size. Contains many whitish and yellowish specks. Liver sprinkled with necrotic foci, involving usually a single lobule. Minute yellow foci in bronchial glands, but lungs not visibly affected. The death of this guinea-pig was premature and probably due to some injury.

Two guinea-pigs were inoculated subsequently with the seventh generation of the serum culture from the lung series.

March 15, 1895. Guinea-pig No. 353, male, weighing 510 grams, receives into subcutis of one side a loop of the growth from a serum culture fifteen days old.

28*th*. A firm tumor about one-quarter inch in diameter at seat of inoculation. No enlargement of kneefold gland yet.

April 12*th*. Local lesion now a small concave ulcer with thickened border and smooth, dry base. Nearest kneefold gland the size of a bean.

May 30*th*. Found dead to-day. (Notes by Dr. V. A. Moore.) Locally no ulcer, but subcutaneous infiltration with a series of caseous glands in kneefold and an eruption of tubercles on peritoneum near site of inoculation. Spleen, liver, and lungs affected. Spleen very large.

March 15*th*. Guinea-pig No. 354, male, weighing 370 grams, is inoculated in precisely the same way as No. 353.

28*th*. Local lesion as in 353. Slight enlargement of kneefold gland.

April 12*th*. Local lesion represented by a large, quite superficial scab with very little subjacent infiltration.

15*th*. Found dead. Kneefold and axillary glands of inoculated side enlarged; contain necrotic foci. Small foci in corresponding glands of opposite side, in cervical, and retro-peritoneal glands. Spleen very large, contains necrotic masses. Liver permeated with yellow masses of dead tissue. Some serum in thorax. Lungs congested. A few gray tubercles in them.

II.

The source of the other culture was a tuberculous bull. The disease was one of long standing. It started in the lungs, and secondary infection of the throat glands and generalized infection had already taken place.

Two guinea-pigs (Nos. 232, 333) were inoculated with small bits of the recently diseased hyperplastic retro-pharyngeal gland on October 20, 1894.

November 28*th*. No. 233 quite ill; chloroformed. On the inoculated side (right) a concave ulcer with caseous base. Nearest glands large, necrotic, firm. Corresponding glands of opposite side contain minute foci. Spleen very large, contains large areas of necrosis in addition to many isolated foci. Fully one-half of liver tissue necrosed. Lungs contain many gray tubercles, a few with necrosed centre.

December 1*st*. No. 232 chloroformed. Lesions less advanced; evidence of a retardation of the disease. Bronchial glands quite large, but lungs free from visible tubercles.

The tuberculous tissue had thus the usual virulence when compared with tissues from a long series of other cattle tested in the same way during the past eight years.

From No. 233 cultures were made on beef's serum. Repeated subsequent examination of the cultures showed that growth had not taken place. Finally on January 19, 1895, one of the serum tubes showed evidence of growth. A considerable number of minute gray-

ish cohesive bodies were found on the surface of the condensation water and in the bottom, none larger than a millimetre in diameter. These were crushed in cover-slips and stained and found to be composed of tubercle bacilli.

The further cultivation of these organisms upon blood-serum was attended with great difficulty. Only the feeblest increase of the transferred bacilli could be noticed on the surface of the serum. More favorable than this was the surface of the condensation water. In a number of tubes delicate patches of growth appeared on this which responded to the specific stain for tubercle bacilli. These patches soon become brownish on the margin, an indication of disintegration.

After many failures to carry the culture beyond the second generation, which in itself was very feeble, I finally succeeded by returning to the original culture, removing some of the minute specks from the surface of the serum and rubbing them upon the surface of some fresh dog's serum. This original culture was now four months old. Within a month after the inoculation of the fresh tubes a very faint ground-glass-like appearance of the surface of the blood-serum could be noticed, which was in fact made up of tubercle bacilli. Thereafter the continuance of the culture presented no special difficulties, although the growth remained quite feeble as compared with the *Nasua* culture.

The success in at last continuing the growth of the bovine tubercle bacillus enabled me to compare its virulence with that of the *Nasua*, presumably human, bacillus directly on cattle.

The latter had already been tried, but with negative result:

November 19, 1894. A yearling bull (No. 296) was inoculated as follows: A feebly clouded suspension of tubercle bacilli from a blood-serum culture of the *Nasua* bacilli nineteen days old was made, and this injected into the thoracic cavity by Dr. Schroeder. The place chosen by him was the space between the sixth and seventh ribs on the left side. The temperature taken twice daily remained normal until February 20, 1895, when the animal was killed. No trace of tuberculosis found.

The experiment was now repeated by inoculating two heifers under as nearly the same conditions as possible; one with the bovine, the other with the *Nasua* culture. At the same time four guinea-pigs were inoculated, both to determine the relative effect of the two

cultures upon them, and to have them serve as controls upon the cultures used. These had been prepared on April 22d by inoculating dog's serum. A fairly satisfactory growth had appeared by May 2d, at which time suspensions were made in sterile bouillon and kept in the cold until May 4th, when the inoculation upon cattle was made. The cultures injected were thus made under precisely the same conditions as to medium and age of growth. The only exception to the uniformity of conditions was that a slightly denser suspension of the *Nasua* bacilli was used for the injection.

May 4th, 1895. Heifer, No. 300, about two and one-half years old. Common stock. In very good condition. To-day this animal received, with a hypodermic syringe, into the right thoracic cavity between the sixth and seventh ribs, 4 c.c. of a suspension of *Nasua* bacilli in sterile bouillon. The inoculation was made by E. C. Schroeder, M.D.V. No symptoms of disease were noticed in this animal and it was killed June 27th, fifty-four days after the inoculation. At the autopsy no lesions were found after a careful search.

May 4th, 1895. Heifer, No. 284, about two and one-half years old. Of common stock and in very good condition. This animal was inoculated precisely as the preceding, with the same quantity of a suspension of the bovine bacilli in bouillon. The suspension in this case contained probably fewer bacilli.[1]

24*th*. Heifer aborted. Fœtus about seven months old.

27*th*. Membranes had to be removed. Heifer has lost appetite and is growing thin and weak.

June 1*st*. Animal extremely weak and emaciated. Expiration accompanied with a grunt. Back arched. Hind legs drawn forward under the body.

6*th*. Heifer rapidly growing worse, but still on her feet.

8*th*. Found dead this morning.

The autopsy notes of Dr. Schroeder show a case of acute miliary tuberculosis. All the lymphatic glands, including those of the limbs (shoulder and flank), were permeated with minute necrotic foci of a pale-yellow color. Some glands, such as those in the thorax, were considerably enlarged, owing to the tuberculous infiltration.

The severest lesions were found in the thorax, as might have been anticipated. The pulmonary pleura of the right side is uniformly but loosely adherent to the ribs and diaphragm, and covered with deposits of minute tubercles. At the seat of the inoculation the pleura is fully one-half inch thick. The right lung is hyperæmic, permeated with small necrotic foci, and does not collapse. The left lung, though not adherent, is in the same condition as the right.

[1] For the notes following I am indebted to Dr. Schroeder, as I left Washington early in May.

The pericardium is completely adherent to the adjacent lung tissue. In the kidney tubercles are numerous in the cortex. The ovaries and udder are apparently normal to the naked eye. In the uterus there is nearly a litre of turbid yellowish fluid of offensive odor. The mucous membrane hyperæmic and streaked with hemorrhagic lines.

Tubercle bacilli were found by Dr. Schroeder in cover-glass preparations of the crushed tissue of several lymph glands.

From portions of tissue reserved for me by Dr. Schroeder and hardened in alcohol, sections were made, and the result of the microscopic examination is in brief, as follows:

The section of lung tissue showed, when viewed with a loop, a large number of tubercular foci quite uniformly scattered over it. They were about one-half mm. in diameter and each presented a small number of darker points, the necrotic centres of the agglomerated tubercles. In each lobule there were twenty or more such agglomerations visible on the cut surface. These tubercles were made up of the usual embryonal connective tissue with a decided tendency toward nuclear disintegration. Giant cells were very rare. Tubercle bacilli numerous.

Sections of one of the mediastinal glands, which was quite large, showed very many tubercles with central necrosis well under way. The tubercle bacilli were exceedingly numerous, but giant cells very rare.

Sections of liver tissue showed a few small tubercles provided with one or more giant cells. The bacilli were also very numerous.

In the kidneys there were numerous tubercular foci, appearing in the main in the cortical portion, sheathing the minute arteries. Giant cells were very rare and tubercle bacilli only occasionally detected.

In sections of the lower superficial cervical gland (shoulder gland) a number of agglomerations of tubercles were present, showing decided central necrosis. Giant cells were rare, but tubercle bacilli exceedingly numerous among the disintegrated nuclei.

The tubercle bacilli were thus most numerous in the lymphatic glands examined and in the lungs, the original place of deposit. They were fairly numerous in the sparse liver tubercles and quite rare in the foci in the kidney. The glands in this case, as in the natural disease, are evidently least able to resist the encroachments of the tubercle bacilli.

As regards the lung disease, I am unable to state whether the countless foci were due to the injection of the suspension into a small air-tube and the dissemination into the alveoli, or whether the main distribution occurred through the bloodvessels.

The case is of interest because miliary tuberculosis in a generalized acute form seems rare in cattle. I have never seen a case myself. It

is probable that the number of bacilli injected is responsible for this form of the disease, inasmuch as they appear to have overpowered the animal before the mechanism of resistance and reaction could be brought into play. This may also account for the general scarcity of giant cells, which embody the reactive power of the individual and which are quite invariably present in the natural disease.

In view of this rather startling difference between the effect of the *Nasua* and the bovine culture upon cattle, it may be claimed that possibly certain conditions may have favored the bovine bacillus, such as pregnancy. While I am not inclined to lay much stress upon this possibility, I hope that the inoculation experiment may be repeated soon, before the prolonged cultivation shall have caused an attenuation or modification of the original virulence.

The results of the comparative inoculations upon guinea-pigs simultaneously with the cattle are also in favor of the greater virulence of the bovine culture. It should be stated here that in testing the comparative pathogenic or invasive power of bacteria the most susceptible animals are of the least value. It is only in the more refractory animals that differences begin to appear which give us a better insight into the degree of virulence or into any specific tendencies.

Nasua culture. (May 3d.) Guinea-pig, No. 382, weighing 312 grams, male, receives subcutaneously 0.5 c.c. of a bouillon suspension of tubercle bacilli. No. 383, weighing 340 grams, male, receives the same dose. No. 382 was found dead on the forty-seventh day. The lesions did not present any marked peculiarities. Besides the local ulcer, the lymph-glands were large, cheesy, but still firm. The spleen is very much enlarged, infiltrated, and has necrotic patches. Liver extensively necrosed. In both lungs a moderate number of tubercles, some with necrotic centre. No. 383 was chloroformed on the fifty-fourth day. The lesions were much less severe, but more advanced, some glands having disintegrated foci. Liver with irregular surface; necrosis slight. Spleen extensively involved. Lungs contain a moderate number of tubercles as in No. 382.

Bovine culture. (May 3d.) Guinea-pig, No. 384, weighing 312 grams, male, receives 0.5 c.c. of a bouillon suspension of tubercle bacilli subcutaneously. No. 385, weighing 340 grams, male, receives the same dose. No. 384 died on the thirty-ninth day. The disease appears on the whole much more intense than in the preceding cases. The spleen, liver, and lungs are severely involved, the local ulcer large. No. 385 died on the thirty-first day with nearly the same lesions, but less pronounced, probably because the disease had run a more rapid course.

Without insisting too much upon these inoculations as indicating a difference in degree of virulence, I still think that in these cases this difference was manifested both by the different life-period after infection and the lesions. Thus: No. 382 (Nasua culture), lived forty-seven days; No. 383 (Nasua culture), chloroformed on fifty-fourth day; No. 384 (bovine culture), lived thirty-nine days; No. 385 (bovine culture), lived thirty-one days.

Nearly a year after these comparative tests the virulence of the two cultures was again tried upon guinea-pigs and rabbits. The bovine and the *Nasua* bacilli had been cultivated on the same substrata, in the same thermostat, and the cultures simultaneously renewed every two or three weeks.

On March 20, 1896, cultures, prepared March 4th on dog's serum and now presenting quite a vigorous growth, were used to make suspensions in sterile bouillon. The suspension of the bovine bacilli consisted of very minute particles, that of the *Nasua* culture of minute and somewhat coarser clumps which it was impossible to reduce.

Rabbit No. 2, weighing 1800 grams, received 0.75 c.c. of the *Nasua* suspension into an ear-vein; rabbit No. 3, weighing 2278 grams, received 0.5 c.c. of the bovine suspension into an ear-vein. The latter was found dead on the sixteenth day, although not manifestly ill beforehand. There was an exquisite, embolic tuberculosis of every part of the lungs. They were densely studded with tuberculous foci, varying in size from mere specks to irregular patches 2 to 3 mm. in diameter. Generalized tuberculosis was manifested by the presence of small foci in the knee-fold and axillary glands and in the kidneys. The spleen was four or five times the normal size, permeated with grayish specks, probably enlarged Malpighian bodies. The liver was large and pale, with a faint yellowish mottling indicative of fatty degeneration.

Rabbit No. 2 remained active until the fifty-fifth day, when it was chloroformed to close the experiment. The only traces of any tuberculous foci found after some search were a minute tubercle on the lateral edge of one of the left lobes, a second 1-mm. translucent tubercle, and a grayish hepatization of the extreme tip in a small lobe of the right lung. This focus was only 2 mm. in diameter. No traces of disease in other organs. Much adipose in abdomen.

The guinea-pigs inoculated at the same time were adults weighing about 500 grams, which, as a rule, show considerable resistance to tuberculosis as compared with younger animals. I shall not enlarge upon this part of the experiment, although the autopsy notes present suggestive features. All the guinea-pigs had been used sometime before to test the strength of diphtheria antitoxin.

Guinea-pig No. 176 received 0.5 c.c. of the bovine suspension, subcutaneous. Guinea-pig No. 171 received 0.2 c.c. of the bovine suspension, intra-abdominal. Guinea-pig No. 102 received 0.75 c.c. of the *Nasua* suspension, subcutaneous. Guinea-pig No. 150 received 0.3 c.c. of the *Nasua* suspension, intra-abdominal.

No. 176 chloroformed on the fifty-fifth day. Very extensive invasion of the lymph glands, lungs, and spleen; liver large, mottled with gray.

No. 171 died on the thirty-third day. Extensive tuberculosis of peritoneum, liver, and lungs.

No. 102 died on the thirty-seventh day. Marked emaciation. Tuberculous changes of liver and spleen slight; lungs free.

No. 150 died on the forty-second day. Moderate tubercle eruption on peritoneum; spleen and liver only slightly affected. Lungs contain many minute tubercles.

The discrepancy between this and the preceding inoculations on guinea-pigs is only apparent. In the *Nasua* animals the internal changes were comparatively slight when compared with those of the bovine cases. The early death of No. 102, associated with marked emaciation, may be due to a more poisonous action of the *Nasua* bacilli or, perhaps, to causes unknown. Further observations must be made on this point.

This experiment reveals a striking difference in the pathogenic power of the bovine and the *Nasua* bacilli on rabbits. It shows as before a greater invasive power toward guinea-pigs coupled with more extensive necrosis of the invaded organs and tissues. The virulence does not appear to have been appreciably reduced by time in case of either culture.

Experiments to determine any difference in the thermal death-point of these cultures have still to be made. They are important from a practical point of view, since there does not exist, up to the present, strict unanimity with reference to the lowest thermal death-point of tubercle bacilli in milk. The greater resistance of the bovine bacilli to the bleaching action of H_2SO_4 leads me to anticipate a greater vital tenacity of these bacilli toward heat.

III.

Nothing has thus far been stated concerning the morphology of these bacilli. This is discussed most easily by comparing them with each other.

Cover-glass preparations from parallel cultures were prepared by staining them for five minutes in carbol-fuchsin and immersing them for about 30-45 seconds in a 10 per cent. (vol.) solution of sulphuric acid.

In serum cultures of the early generations about two weeks old the *Nasua* bacilli were quite uniform in size, about 2 μ long and slightly curved. In cultures five to six weeks old the bacilli had lost the regular outline to some extent. More deeply stained, roundish bodies appeared within them, though not regularly so, and slightly distended them. They were also longer, fully 3 μ at this time.

On glycerin bouillon cultures three weeks old the bacilli were, perhaps, a trifle larger than those on serum. Some were irregular and contained occasional bodies more deeply stained.

The bovine culture presented some features quite different from those of the *Nasua* culture. In cultures about two weeks old the bacilli taken from the condensation water of serum tubes were nearly straight rods not more than 1 to 1.5 μ in length, and about as thick as the *Nasua* bacilli. Many bacilli were swollen in the centre or at one end and approached oval cocci in appearance. Degeneration was manifest. In the original culture from the guinea-pig two-and-a-half months old the bacilli appeared now 2 to 3 μ long. They were quite thick and not distinguishable readily from the *Nasua* bacilli.

In later parallel cultures the morphological differences were more defined, and therefore more striking. Cultures on dog's serum started October 12, 1895, were examined November 2d. These cultures represented the eleventh of the bovine and the fifteenth of the *Nasua* series, the date of the original *Nasua* culture being July 17, 1894, of the bovine, November 28, 1894.

Cover-glass preparations dried, heated, stained in carbol-fuchsin and decolorized in H_2SO_4, presented the following features (see Plate):

Bovine bacilli, short, straight, deeply stained rods, averaging 1 μ in length and varying perhaps from 0.8 to 1.2 μ With a magnification of 1000 diameters the rods were shown to be not very regular in outline. In some, one end tapered slightly; in others, the central portion was slightly swollen. The bacilli were in masses or clumps; isolated ones not very abundant. Stain held after an exposure to H_2SO_4 for thirty and sixty seconds.

The *Nasua* bacilli are slender and more or less curved rods like the

arc of a circle. They adhere to one another, side by side, in the usual, well-known manner. In length they varied between 2 and 4 μ, the majority being about 3 μ. In outline they were not very regular, ends somewhat tapering. Staining well retained after an immersion of thirty seconds in H_2SO_4. Partial discoloration after an immersion of sixty seconds.

In this brief description it will be noted that the bacilli in these two cultures differ in form, length, and in the capacity to retain the stain in acids. These differences have thus maintained themselves, and have become more accentuated, within the period of a year. Anyone after one examination would be able to recognize one from the other culture. It is not a difference of more or less, but one of kind.

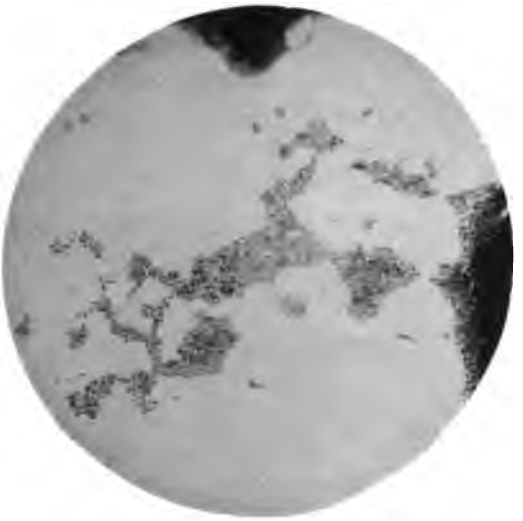
Parallel cultures on dog's serum were again compared February 12, 1896, when eight days old. In these the same differences were present. No change had taken place.

At this time the growths on the surface of the serum were easily distinguishable from each other with the unaided eye. The *Nasua* culture had a decidedly whitish cast where the masses of bacilli transferred had become enlarged into clumps by continued growth. They were not easily broken up, but when transferred to fresh serum persisted in cohering in little balls. The bovine culture spread more evenly over the serum and formed an inconspicuous membrane having the appearance of ground-glass. The platinum loop, passed over the surface, brings with it a soft mass having little cohesion and easily spread out on a fresh surface.

These differences are of minor significance, yet they are of some value since all other factors likely to cause differences were eliminated by a strict uniformity of conditions. It will thus be seen that the bovine bacilli were different from the *Nasua* bacilli in nearly every culture examined, in being shorter and not curved. This difference was also manifest in preparations of a bovine culture isolated in 1886, which were restained for this purpose. Furthermore, bacilli from a culture of human tuberculosis from Dr. Trudeau closely resembled the *Nasua* bacilli and differed from the bovine bacilli.

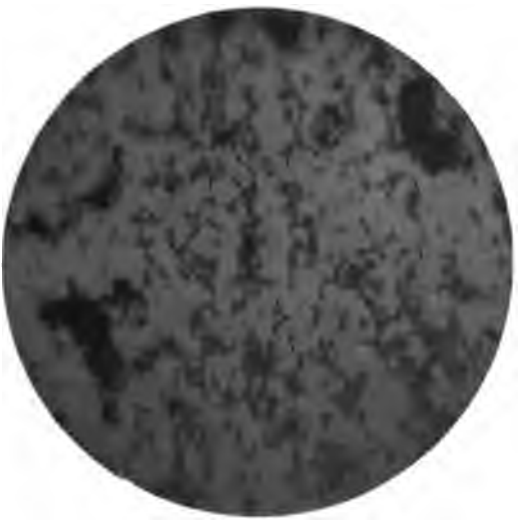
A number of important questions are raised by these observations. Of these, only that one concerns us here which deals with the relation between human and bovine tuberculosis and the transmission of the latter to man. This question may be put in the following form:

FIG. 1.



Bovine bacilli from a dog's serum-culture of the eleventh transfer. The slide was prepared November 2, 1895, from a culture twenty-one days old. Stained in carbol-fuchsin and decolorized in 10 per cent. (by volume) of sulphuric acid. Mounted in balsam.

FIG. 2.



Nasua bacilli from a parallel culture on one of the same lot of serum-tubes. Dates and staining as for Fig. 1. Fifteenth transfer.

Negatives by Mr. Simeon C. Keith, Mass. Institute of Technology. × 500.

Are cattle attacked by different races of tubercle bacilli, or is there but one race adapted to the bovine body?

Koch, in his deservedly renowned monograph, states that he cultivated through a number of generations tubercle bacilli from eleven head of cattle. Of these, four were obtained directly and seven indirectly through guinea-pigs. He tacitly regards these as identical with those isolated from man and other mammalia, and we have no reason whatever to doubt his observation or judgment on this subject. Kruse and Pansini, already quoted, describe what appear to be avian bacilli isolated from cattle.

Observers, everywhere, have experienced great difficulty in obtaining cultures of tubercle bacilli from man and animals. Only occasionally have they been successful. This may be ascribed either to want of skill in observing the precise conditions necessary in the cultivations or else to an initial difference in the bacilli themselves in virtue of which some may be cultivated, others not. I am inclined to the second explanation, namely, that bacilli differ. The cultures which I have described demonstrate this in an unmistakable manner. Unless this were so, it would be difficult to explain why in bovine cultures made in 1886 I should have obtained cultures from two organs of the same guinea-pig, and why this same thing should have happened in the *Nasua* cultures. And yet in spite of very numerous efforts I have obtained during the past eight years only these two cultures from guinea-pigs which had been inoculated with tuberculous tissue from cattle. It would appear from the publication cited that slightly different races of tubercle bacilli have been obtained from cattle. It is, however, not possible to determine definitely whether or not some of the easily cultivated and more or less attenuated bacilli were responsible for the disease process and not accidentally present. Any tubercle bacilli isolated from cattle which do not produce tuberculosis in guinea-pigs should arouse our suspicion, since tuberculous tissue from cattle has always produced a generalized disease in guinea-pigs.

It is difficult to assign any trustworthy value to differences manifested on culture media when the length of time during which the bacilli have been subjected to artificial cultivation is not known. Whatever value may be attached to differences manifested by absence of growth on one medium and a vigorous growth on another must be

derived from the earliest generations, owing to the peculiar adaptation which the tubercle bacillus undergoes. Thus the bacilli obtained from Dr. Trudeau failed in a number of trials to grow upon blood-serum, while the *Nasua* bacilli in parallel cultures did just the reverse; they grew well upon beef's and dog's serum, but very feebly on glycerin agar. This difference might be considered sufficient to establish a variety, but I believe that it is due to the slow adaptation to certain culture media (agar) by which the power to grow on other media (blood-serum) is forfeited. This may, perhaps, account for the difference observed by Trudeau between two cultures.[1] One had been isolated by him from the lungs in a case of miliary tuberculosis, and had passed through three generations only. The history of the other culture was unknown, but it was regarded as an old one. The first culture grew typically upon glycerin agar in the form of dry scales, and abundantly upon potato. The growth of the second upon glycerin agar had the consistency of thick cream. Upon potato it failed to grow. This failure may have been the result of slow adaptation to glycerin agar.

If we were to take as guides the behavior of the earliest generations of tubercle bacilli toward different carefully and uniformly prepared substrata, some important facts might thereby be gathered on the different degrees of saprophytism manifested by the tubercle bacillus. That such degrees exist is demonstrated by the two cultures I have described. It may also be read between the lines of the writings of others. Thus Weyl[2] describes a successful culture on glycerin agar directly from the tuberculous spleen of a dog. Kitasato obtained cultures on the same medium directly from sputum which grew at first atypically, but typically after four weeks.[3]

Passing now to differences in the manifestations of the human and the bovine disease, we have at the outset the name *Perlsucht* to emphasize a difference which is perceived by the naked eye. The nodular affections of the serous membranes strongly remind one of affections due to animal parasites. Next comes the predilection of the disease for lymph glands, as in the tuberculosis of infants and children. The lung tissue is in many cases intact, so also the intestines, though the

[1] Proc. N. Y. Path. Society, 1890, p. 75.
[2] Centralblatt f. Bakteriologie, vi. (1889) p. 689.
[3] Zeitschrift f. Hygiene, xi. No. 3.

bacilli have evidently passed through them to the associated glands. In the bovine disease,[1] the lung disease starts, as a rule, in the large caudal lobes, those in which we might suppose the tubercle bacilli to be deposited most easily. In the human adult the cephalic lobes, in which we might suppose the fewest bacilli to be deposited, are most commonly the seat of the disease. Any catarrh of the air-tubes does not precede lung infections in cattle, although this is started up after the tubercles begin to bulge into and partly occlude the lumen of the affected air-tube. The tubercle bacilli of cattle are, furthermore, not inclined to multiply in the catarrhal secretions of the air-tubes or the bronchiectatic cavities found so often in lungs extensively involved. An examination of the muco-purulent contents of air-tubes frequently fails to reveal tubercle bacilli, though there may be advanced disease.[2] This indicates a less saprophytic tendency than is manifested by the bacilli in human tuberculosis. In fact, it would seem that with the continued opportunity afforded by the human tubercle bacillus to multiply in the products of cavities and air-tubes, practically shielded from any adverse influence of the body cells and fluids, and with the opportunity which such bacilli have of being transmitted frequently from person to person, varieties of bacilli might arise requiring special conditions, such as bronchial catarrh, for their successful location and further multiplication.

Differences between human and bovine tubercle bacilli might thus be predicated from the differences manifested by the disease process. Any claim which maintains that the difference is due to soil and not to the bacilli is one-sided, because it overlooks the biological fact that the effect is mutual, and that change of soil or environment means in the end modification of the organism and the formation of varieties. The great sensitiveness of the tubercle bacillus to change of media, the difficulty, in other words, of getting an artificial growth started, signifies that the transmission of certain bacilli from one species to another might encounter obstacles still greater than in the culture tube. Again, the tubercle bacillus is properly regarded as a parasitic organism, rather highly specialized toward an intracellular existence. It is a well-

[1] Theobald Smith: "Studies in Bovine Tuberculosis." Bulletin No. 8, Bureau of Animal Industry, U. S. Department of Agriculture (1894), pp. 88–126.

[2] In glancing over the recently published report of the Royal Commission on Bovine Tuberculosis, I noticed that McFadyean has made the same observation.

known law that the more specially fitted to certain environments the organism, the less likely is it to survive or take root outside of those conditions. This is particularly true of protozoa. Thus the hæmatozoa of malaria fail to develop in the lower animals. Those of Texas fever, though extremely virulent to cattle, are harmless to other animals. The same may be true to a less degree of the tubercle bacillus. Virulence toward one species in such organisms is no criterion of its invasive power toward other species. This must be determined experimentally or by the absolute identification of the causative organisms in the two allied diseases.

This subject has to-day assumed considerable importance, owing to the possible transmission of tuberculosis from cattle to man. That much of the tuberculosis of infancy is due to infected milk is urged from many quarters, and much perturbation in the public mind has been caused by it. I have endeavored to trace in the recent literature of this subject some evidence for or against the claim. Kossel[1] reports upon twenty-two cases of fatal tuberculosis in which the lung infection predominated, and in which an independent tuberculosis of the digestive tract appeared in but one case. In fourteen other cases in which death was due to other causes, caseous foci were found in the bronchial glands in ten, in the mesenteric glands in four cases. Bearing in mind the habit of infants and children to put things of all sorts into their mouths, an infected environment would furnish as good an opportunity for food infection as milk. Kossel does not even touch upon the possibilities of infection through milk, but has merely collected evidence concerning the surroundings.

I have presented this subject, not as an advocate for or against the view that milk is the cause of much or little tuberculosis, but to call attention to the necessity for more information along the following lines:

1. The existence of races of tubercle bacilli (both human and bovine).

2. The identity or non-identity of bovine and human tubercle bacilli.

3. The effect of bovine tubercle bacilli on man. This problem could be attacked by cultivating bacilli from a case of tuberculosis contracted by drinking milk, and testing them on cattle.

[1] Ueber Tuberkulose im frühen Kindesalter. Zeitschrift f. Hygiene, xxi. (1895) p. 59.

4. More evidence on the subject of milk infection by tracing the source of the disease in infancy more carefully, and by searching for primary foci of tubercular infection at all autopsies on children.

5. Any existing difference between the disease produced in early life by human and that presumably due to bovine tubercle bacilli.

It seems to me that the time has come for the medical profession to probe this subject of milk infection more thoroughly, and for this purpose clinical, pathological, and bacteriological workers must unite in order to be successful.

DISCUSSION.

DR. VAUGHAN: I want to compliment Dr. Smith on the most excellent work he has done. If I may be pardoned for saying it, there is a little personal gratification in this. In 1888, when the first edition of my work on ptomaïnes appeared, I suggested that we should not rely altogether on the morphology of germs, but that we must also study their physiology and chemistry. I did not even then go far enough, because I made an exception in the case of the tubercle bacillus. I thought we would find this bacillus without any morphological variation. For suggesting these things I was pronounced a heretic in the bacteriological ranks. Now the evidence is constantly increasing that my position was right. I do not see why we could have disbelieved this at any time. When the higher plants are so modified by the conditions in which they grow, it really seems superfluous to say that these microscopic vegetables could not be altered by like conditions. It is barely possible that sometimes a tubercle bacillus may be found which may aid us in vaccination. This alone should lead us to experiment with tubercle bacilli of all kinds.

I think that Dr. Smith will agree with me that all experiments with reference to the sterilization of milk containing tubercle bacilli should be conducted with milk from tuberculous animals and containing the tubercle bacillus. The experiments made by the addition of human tubercle bacilli to the milk are not so reliable, and we may fall into error. We have plenty of samples of milk containing tubercle bacilli with which to experiment.

DR. PEPPER: I arise to attest my debt of gratitude to Dr. Vaughan for his early work in this matter, for the help that I have derived in clinical work from the suggestions which he made in his early publications. It has seemed to me to be of vital moment that we should recognize not only the different degrees of susceptibility of soil, but also the probability of this immense diversity of virulence of bacteria, which, so far as we have yet gone, judging

solely from the morphological standpoint and response to different stains, must be regarded as coming under the same species. I think this paper of Dr. Smith is of the highest degree of importance as carrying this matter a step further. Why we should not have expected to find the widest range of morbid activity in these different species is indeed strange. I believe that the future of bacteriological investigation holds a vast amount of promise in this direction.

DR. STERNBERG: I would like to ask Dr. Smith if he has ever observed a branching form of the tubercle bacillus described by some bacteriologists, and whether inoculations of human tuberculosis give rise to tuberculosis in cattle.

DR. A. C. ABBOTT: Variability of species is one of the topics of the day in bacteriological work. The evidence that is rapidly accruing seems to justify the prediction that bacteriologists will shortly direct their attention more to the grouping of bacteria than to their identification and definite species, as hitherto.

The most conspicuous variations are probably those concerning the different grades of pathogenesis, though both morphological and cultural departures from normal or fixed types are also seen from time to time.

An important illustration of the variation that occurs in pathogenic species is seen in the bacillus diphtheriæ and its allied forms, that have been known by some as pseudo-diphtheria bacilli.

For a long time the diagnostic feature of the true diphtheria bacillus was considered to be its power of killing guinea-pigs, with characteristic lesions. Any organism that did not possess this property was considered as non-diphtheritic or pseudo-diphtheritic. We now know that the genuine diphtheria bacillus may present all grades of virulence, and, while frequently incapable of destroying the life of a guinea-pig, may still cause local lesions, indistinguishable, save in degrees, from those of the fully virulent organism.

Analogous variations in the colon bacillus, the cholera spirillum, the pyogenic cocci, and others, indicate that these varieties as manifestations must be grouped, rather than classified as distinct, separate species.

DR. THEOBALD SMITH: In regard to the subject of variation, I believe that I was the first one to demonstrate the existence of varieties among pathogenic bacteria, as far back as 1886. That subject has been a favorite one of mine ever since. I think those of us who have grown up with bacteriology know what a strong influence was exerted upon our conception of the fixity of species by reading the publications of the Koch school. That influence must be still stronger upon those who were educated in Berlin. Fortunately the French school exerted the opposite tendency. They have gone to the other extreme, and have become to a certain extent incapable of differentiating organisms and classifying them properly, so that mistakes are made now and then under the general conception of the variability of micro-organisms.

In regard to the question of testing the death-point of tubercle bacilli in milk, I would say that the recent report of the Royal Commission on Tuberculosis in England, just published, contains experiments made with milk from cows with tuberculous udders.

I have never seen the branching form of the tubercle bacillus.

In regard to the inoculation of human tubercle bacilli on cattle, I would say that in the course of the work carried on by the Bureau of Animal Industry many experiments have been made with a culture of human tubercle bacilli without any effect.

What has struck me particularly in the two cultures described is the difference in morphology. Ordinarily we cannot distinguish certain bacteria under the microscope which differ in physiological characters, but here we can recognize the difference with the microscope and have also a decided difference in virulence.

REPORT OF A CASE OF INDIGENOUS PARASITIC CHYLURIA WITH FILARIA NOCTURNA IN THE BLOOD.

By FREDERICK P. HENRY, M.D.,
OF PHILADELPHIA;
PROFESSOR OF THE PRINCIPLES AND PRACTICE OF MEDICINE IN THE WOMAN'S MEDICAL COLLEGE OF PENNSYLVANIA.

FANNY B., married, aged twenty-nine years, was born in Columbia, S. C., and spent the first twenty-seven years of her life in that town. Her twenty-eighth year was passed in Palatka, Fla., and her twenty-ninth in Philadelphia, where she arrived in Mareh, 1895. Her father died from sunstroke, and her mother, for several years before her death, suffered from "shingles"—herpes circinatus.

She had the usual diseases of childhood, except scarlatina. At the age of twelve she fell from a fig tree, and soon after developed a large abscess in the left lumbar region, the site of which is plainly indicated by a cicatrix about three inches long, a little above and parallel with the posterior portion of the crest of the ilium. This abscess continued open for several months, but finally healed. A year after its closure another abscess appeared in the left iliac region, and also pursued a chronic course. Its site is indicated by a linear cicatrix about two inches long, a little above and parallel with Poupart's ligament. The patient suffered from what she vaguely described as an attack of malarial fever in March, 1895, but never manifested any signs of malarial infection while in the South. She has had two miscarriages: one at four months and a half, the other at two months. Both were ascribed to persistent vomiting.

Three weeks before her admission to the Woman's Hospital of Philadelphia—she was admitted on February 16, 1896—she gave birth to a child at term. The labor was natural in all respects. Previous to the birth of her child she suffered from pain in the region of the kidneys. On the second day of her lying-in this pain became intense and continued for a week, when it abated somewhat. On admission it was still complained of. On the third day of her lying-in she passed milky urine, and had difficulty in micturition on account of the occlusion of the urethra with what she regarded as stringy masses of mucus. They were, in reality, coagula of lymph and blood. The urine, after standing for several hours in a narrow, cylindrical

vessel, separates into two portions, of which the lower is distinctly hemorrhagic; while the upper has the appearance of milk or cream. Floating on the upper chylous layer are numerous coagula of a delicate, pinkish hue, and almost translucent, while at the bottom are a few small blood-clots. A little of the urine was shaken up in a test-tube with ether and set aside until the urine and ether had separated. The latter being then evaporated on a watch-glass, a distinct deposit of fat was obtained. The chylous urine contained a trace of albumin, but no sugar, and was free from casts.

I found this woman awaiting me at my clinic at the Woman's Hospital on Tuesday, February 18, 1896, and lectured upon her case as one of chyluria, probably parasitic. On the evening of February 19th I visited the hospital for the purpose of examining my patient's blood for the filaria sanguinis, taking with me a small microscope and making the search with a half-inch objective. I withdrew the blood from the finger about 10 P.M., and examined several slides without finding the parasite. I left the slides at the hospital, and after my departure one of the resident physicians, Dr. Ida E. Blackburn, examined them with a stronger lens, and fortunately succeeded in detecting the filaria. Since then filariæ have been found in almost every slide examined. They are not numerous, the maximum number observed on a single slide being five. The urine was repeatedly examined, the centrifugal machine being used to separate the parasites, but only on one occasion were they found in that fluid. With the specimen in which they were detected the centrifugal machine was not employed. The filariæ have not been found in the milk of the mother or in the blood of the infant, and they are very few in number or absent from the blood of the mother during the day. The variety present in this case is, therefore, the filaria nocturna, the embryo of an adult which is alive in one of the lymphatic channels.

The patient was put to bed, and frequent examinations were made of her blood and urine. She was at first placed upon quinine and ergotin, without any apparent effect, the urine continuing chylous and bloody, although in an intermittent manner. February 25th I examined the blood, and found filariæ. I then directed leeches to be applied to the lumbar region, ostensibly to relieve pain, but in reality to test the question whether the leech might play the *rôle* of an intermediate host to the filariæ. Three of the leeches were sent to me the next morning. I opened one of the leeches at 10 A.M., and examined its blood. Filariæ were abundantly present—one slide contained six—and actively moving. The next morning (February 26th) they were still active. The same afternoon I found three dead filariæ on one of the slides, and but one still living and languidly moving. At the same hour the filariæ removed directly from the body were all living. On February 29th I opened another leech, and found a number of dead filariæ in its blood—none living. It appears evident, therefore, that although the filariæ may live many hours in the body of the leech, that animal does not play the part of an intermediary host to them.

Feb. 28th. The patient was placed upon thymol (gr. ij every three hours), and coincidently with its administration the urine became normal in every respect, and so continued for seven days, when it again became chylous and bloody. The filariæ during this interval were abundantly present in the blood.

March 12th. I ordered methylene blue in two-grain capsules every three hours, being induced to do so by the remarkable statements of Dr. Austin Flint concerning the efficacy of this substance in a case of parasitic chyluria.[1]

13th. I found Mrs. B. out of bed and dressed. Her appearance was good, her lips and cheeks being well-colored; urine deep blue; eye-ground examined by Dr. Gertrude A. Walker, ophthalmologist to the hospital, who confirmed my observations as to the absence of any morbid appearance in the retina. Patient anxious to go home, but persuaded to stay another week.

On Saturday evening, March 14th, I obtained some blood from the finger as usual, and examined it the next morning. I had scarcely placed the first slide under the microscope when I detected two filariæ (in the same field) moving with the greatest activity. I was unable to perceive that the filariæ were stained in the slightest degree by the methylene blue which the patient, at the time the blood was withdrawn, had been taking continuously for seventy-two hours. Her urine and feces were stained a deep blue, but *the milk was uncolored.*

Thus far I find no corroboration of Flint's statement that methylene blue stains the filariæ in the circulating blood, much less that it exerts any deleterious influence upon them. My experience, although differing from that of Flint in this matter, is precisely in accord with that of Laveran,[2] who found that the filaria perished a few seconds after it was brought into contact with a drop of a solution of quinine of the strength of 1–1000, while methylene blue (strength of solution not stated) does not hasten their death, and does not stain them until they are dead.

17th. Mrs. B. came downstairs to my clinic at the Woman's Hospital; specimen of her urine deeply stained with methylene blue exhibited. Blood was withdrawn from her finger at one o'clock, and seven slides prepared. These were repeatedly examined by myself and an assistant, the result being that two filariæ were found in the seven slides. This is the third time in which the blood has been examined by day, namely, once before at one o'clock, when no filariæ were found, and once at 8 A.M., when only one was discovered. It is evident that the parasites are much less numerous in the superficial capillaries by day than by night. This is the sixth day since the

[1] New York Medical Journal, June 15, 1895.

[2] Bulletins et Mémoires de la Soc. Méd. des hôpitaux de Paris, 3 série, tome x. p. 738.

treatment with methylene blue was instituted, and the results thus far are by no means encouraging. The drug appears to be absolutely inert, so far as concerns the destruction of the filariæ. Different opinions as to whether or not the filariæ were stained were expressed by those who saw the specimens. The majority thought they were not, but being on the lookout for such staining, I *fancied* that they had a faint bluish tinge.

19*th*. At one o'clock, the patient having been taking methylene blue (two grains every three hours) for one week, I counted the blood corpuscles. Number of red corpuscles per cubic millimetre, 4,100,000, white not increased in number and *unstained*. Hæmoglobin 65 per cent. Five slides of rapidly dried blood were prepared, and no filariæ found. It is a singular fact that the previous day, while the patient was taking the methylene blue as usual, the urine suddenly became quite clear and macroscopically normal. I gave two slides of blood to Dr. Alfred Stengel, of the Pepper Laboratory of Clinical Medicine (University of Pennsylvania), in order to obtain his opinion as to whether or not the leucocytes were stained with the methylene blue which the patient had been taking continuously in full doses for more than one week at the time the blood was withdrawn. Dr. Stengel reported that he could find no evidence of blue discoloration of the corpuscles.

20*th*. At nine o'clock in the evening I prepared a number of slides. The filariæ were abundantly present. I found them in eighteen out of twenty-one preparations, and, as I did not use a mechanical stage, it is possible that I may have overlooked them in the three slides in which the search was ineffectual. The serum of the blood was decidedly blue and the filariæ of an exceedingly delicate bluish tinge. The methylene blue had been taken by the patient continuously in full doses for nine days and had proved absolutely inert, so far as any influence upon the vitality of the embryos is concerned.

21*st*. The patient returned to her home.

I omitted to state that shortly after the patient's admission I had her vaccinated on the theory that an intercurrent infection might destroy the parasite. The vaccination was perfectly successful, but quite as useless from a therapeutic standpoint as the methylene blue.

The above case is of special interest both because it is the first of the kind observed in Philadelphia, and also for the reason that it adds another to the list of those indigenous to the United States. It is impossible to say how long the filarial embryos have been circulating in the blood of this patient, but it is in the highest degree probable that the infection occurred either in South Carolina or Florida, and it is not impossible that the lumbar and inguinal abscesses from which she suffered at the age of twelve were due to the filariæ. Similar abscesses form part of the clinical history of filariasis. The exciting cause of the chyluria was probably the rupture of a dilated lymphatic during

the expulsive pains of labor. The supposition that infection occurred at the age of twelve or earlier necessarily implies the circulation of the embryos in the blood for many years without giving rise to symptoms. In connection with this question of the innocuous presence of the filariæ in the blood of man, the following case is of interest:

In the autumn of 1893 a well-known physician of Philadelphia consulted me about his son-in-law, who had resided for some years in Columbia, S. C., and latterly near Tampa, Fla. Filariæ were said to have been found in his blood by de Saussure, of Charleston. Up to the time I speak of the symptoms had been those of intestinal indigestion, consisting chiefly of great abdominal distress, meteorism, irregular action of the bowels, great nervous excitement at times, *especially toward evening*. I examined the patient's blood in vain for the filaria, and Professor Guiteras, who examined it twice, was equally unsuccessful. The time of my examination was 10 P.M., and I have since thought that my failure to detect the parasite may have been due to the fact that the patient walked to my office. The gentleman in question returned to his home in Florida, and a few months later passed chylous urine for the first time. The chyluria continued for one or two months and has not returned. Of late the patient has been in a fair state of health, free from the intestinal symptoms above mentioned.

Post-mortem examination of those who have perished from parasitic chyluria has revealed enormous distention of the lymphatic vessels of the urinary tract, and sometimes also of the thoracic duct. A few months ago, I exhibited before the Philadelphia County Medical Society a specimen of chyluria from a Cuban whose blood I vainly searched for the filaria. I had but one opportunity of examining the blood of this man, and for that I was indebted to Dr. Charles W. Coburn, who was in attendance upon the case. Shortly after my examination the man died and an autopsy was held under very unpropitious circumstances. There was, however, no difficulty in ascertaining that the lymphatic vessels, especially those of both renal regions, were enormously dilated and convoluted, many of them being of the calibre of an ordinary lead pencil. The dilatation was most marked on the right side, and in the pelvis of the corresponding kidney there was a pale lymph clot similar to the coagula passed with the urine during life. In this case it is greatly to be regretted that a careful dissection with a view to the detection of one or more of the adult filariæ was not possible. The time at our disposal was limited, and the light was derived from a single lamp which was held by turns by Dr. Coburn and

myself, the autopsy being skilfully performed by Dr. Bundy of the Women's Medical College of Pennsylvania.

The importation of a case of filariasis into a city of the latitude of Philadelphia naturally raises the question whether the disease may become endemic therein, and there seems to be no good reason why it should not. The brilliant researches of Dr. Patrick Manson have established the fact that the mosquito plays the part of an intermediary host in conveying the *filaria nocturna* from man to man. At night the embryos swarm to the surface, while during the day they retire to the deeper vessels. Acting upon this knowledge, Manson exposed a filaria patient to the bites of mosquitoes, and found the embryos in the bodies of these insects, in which, in the course of from five to seven days, they attained a length of one-fifteenth of an inch. In the blood of man, they measure from $\frac{1}{70}$ to $\frac{1}{80}$ of an inch, and are enclosed in a sheath, from which they make their escape in the viscid blood of the mosquito. The mosquitoes with the embryonic filariæ in their interior seek water in which to deposit their eggs. This function accomplished, they perish; the embryonic filariæ are liberated, and through the medium of the water in which they exist gain access to the human system. One or more of the ingested parasites attains maturity in the lymphatic system and continues for an indefinite period (in some cases for many years) to produce swarms of embryos. The latter being but $\frac{1}{3500}$ of an inch in diameter, readily traverse the lymphatic glands, and reach the bloodvessels *via* the thoracic duct. It is through the plugging of the lymphatic vessels, especially those connected with the urinary tract, that the lymph and chyle become mingled with the urine. For further details concerning the life-history of this parasite, and the mode in which it occludes the lymph channels, the reader is referred to the writings of Manson.[1]

In Philadelphia, mosquitoes are abundantly present during the summer and autumn, and have convenient access to the Schuylkill River, from which our water-supply is derived. The chance of a given individual becoming infected through the medium of a river of the volume of the Schuylkill is doubtless infinitesimal, but no one acquainted with the wonderful vitality of the embryonic filaria can deny its possibility.

[1] Especially the articles in Davidson's "Hygiene and Diseases of Warm Climates;" International Clinics, April, 1895; "Transactions of the International Congress of Hygiene and Demography," Seventh Congress, 1891.

The surest safeguard against this and other sources of infection is filtration.

The *filaria nocturna* is now known to be indigenous in Europe, as appears from the report of a case recently studied by M. Font, of Spain.[1] The patient was a man, thirty-five years of age, who had resided all his life at Canet de Mar, with the exception of a short period passed at San Sebastian and Vitoria. Canet de Mar is a town of 5000 inhabitants on the shore of the Mediterranean, in latitude 41° 37′ north, between Barcelona and the French frontier, and is a favorite retreat for veteran sailors, many of whom have visited the West India Islands. Dr. Ballester, in a communication to Font, reports having seen in the same town two cases of hæmatochyluria during fourteen years, in neither of which was there an examination of the blood. In Font's case the presence of the *filaria nocturna* was repeatedly demonstrated.

Thus far three species of filaria have been certainly detected: (1) *Filaria diurna*, (2) *Filaria nocturna*, (3) *Filaria perstans*. These names are indicative of the habits of the animals, *filaria diurna* being found in the superficial vessels solely orchie fly during the day; the *filaria nocturna* solely or chiefly during the night; while the *filaria perstans* is constantly present in the capillaries of the integument. The *filaria diurna* and the *filaria perstans* are confined, thus far, to the west coast of Africa and adjoining districts; while the *filaria nocturna* is pandemic in the tropics and endemic in certain sections of the United States. The adults of *filaria nocturna* have been frequently found; that of *filaria perstans* never, so far as I have been able to ascertain. In the opinion of Manson the *filaria loa* of the eye of the negro of Old Calabar is probably the adult form of the *filaria diurna*. If it is not, he argues, then there must be another blood worm yet to be discovered, for the embryos of the *loa* must escape from the body of their host through the medium of the circulation. The *filaria perstans* has been practically proved by Manson to be the cause of the fatal "sleeping sickness" of the Congo region.

While engaged in writing this article my attention was called by Dr. Charles A. Oliver, of Philadelphia, to a remarkable case of *filaria loa* recently reported by Dr. Argyll Robertson. The patient was a

[1] Revista de Ciencias Medicas de Barcelona, 25 February and 10 March, 1894.

lady who had spent eight years in missionary work at Old Calabar on the west coast of Africa. Without entering into the details of this interesting case I will merely state that in two successive operations Dr. Robertson extracted two *filariæ* (variety *loa*) from the ocular tissues, the first a male, the second a female. Both of these adult parasites are described by Manson in the course of Robertson's paper. The female was stuffed with embryos, but repeated examinations of the blood failed to detect any embryonic filariæ in that fluid. The latter fact certainly seems to refute Dr. Manson's hypothesis that the *filaria loa* is the adult form of the embryonic *filaria diurna*.

In a letter recently received from Dr. Manson, he says that America possesses the

"unenviable distinction of possessing a filaria of the blood, which is possibly peculiar to itself. I found it in negroes from the island of St. Vincent, and I have little doubt that it could be found in the negroes of the more tropical States of the Union. This filaria I have named *Filaria Demarquayi*, after Demarquay, the discoverer of *filaria nocturna*. It is a very small worm, not half the size of the filaria you are familiar with. It observes no periodicity; it is sharp-tailed, and it possesses a sheath," etc.

This *Filaria Demarquayi*[1] should, therefore, be added to the list above given so that, at the present time, there are four distinct varieties of *filaria sanguinis hominis*.

The steps by which our present knowledge of the *filaria nocturna* has been obtained were gradual. The embryo was first discovered by Demarquay in 1863 in the liquid of a chylous hydrocele; next in the blood by T. R. Lewis, of India, in 1872. In 1876, the adult parasite was found in a lymphatic abscess of the arm by Brancroft, of Brisbane, Australia, and is accordingly known to helminthologists as the *filaria Bancrofti*, this name having been assigned to it by Cobbold. Finally, our knowledge of the life-history of the parasite has been completed by the genius of Manson. We are irresistibly reminded of the analogous history of the discovery of trichiniasis, with which the names of Hilton, Paget, Owen, Leidy, and Zenker are associated.

In the United States filariasis can no longer be considered as an extremely rare disease. and it is probable that it is more prevalent in

[1] I would suggest that the last-mentioned parasite would be much more appropriately called filaria Mansoni.

certain of our Southern States than is suspected. Professor John Guiteras, of the University of Pennsylvania, was the first to demonstrate the existence of endemic parasitic chyluria in this country,[1] and de Saussure,[2] of Charleston, has published the clinical histories of twenty-two cases of filariasis observed in Charleston, S. C., from 1886 to 1890. Two cases of filariasis indigenous to Virginia have been reported by Dr. R. M. Slaughter,[3] but in neither of them was the blood examined. In both hæmatochyluria and filariæ were found in the urine, and in one filariæ were found in the pus of an alveolar abscess. While I believe these cases of Dr. Slaughter to be genuine examples of filariasis, I cannot refrain from the criticism that the illustration accompanying his paper bears but a superficial resemblance to the embryonic *filaria nocturna*.

Another indigenous case is reported by Dr. C. W. Mastin, of Mobile, Ala.,[4] the patient being a young man, aged twenty-two years, who had never been outside of Mobile and its immediate vicinity. In Mastin's case the filarious lesion was a chylous hydrocele. The filaria is also said to have been found by Weiss in the urine of a child who had never been out of Illinois.[5] I am by no means sure that I have collected all the reported cases of indigenous filariasis; in fact, I have made no attempt to do so. Sufficient, however, has been said to show that the disease is widespread and not confined to tropical and subtropical regions.

In this connection I may remark that the embryonic *filaria nocturna* is capable of great resistance to cold. My slides prepared in winter and kept in a cold room showed the parasites active at the end of six or seven days; in fact, one lived for ten days. Exposure for many hours to a freezing temperature does not kill them, as proved by one of the methods employed by Manson to demonstrate "filarial ecdysis." This consists in placing the slide containing the filariæ upon a block of ice over night, in order to cause a separation of hæmoglobin from the red corpuscles. The effect of this degree of cold is to render the movements of the animal somewhat languid, but after withdrawal from the ice they become as active as before, and the embryos speedily escape from their sheaths.

[1] Medical News, April 10, 1886.
[2] Ibid., June 28, 1890.
[3] Ibid., September 5, 1891.
[4] Annals of Surgery, 1888, vol. 8, p. 320.
[5] American Text-book of the Diseases of Children, Starr.

Facts such as the above seem to prove that nothing but time is needed for filariasis, the scourge of certain tropical countries, to become prevalent in our town, and demonstrate the vital importance of municipal filtration of our water-supply.

I have said little about treatment in the foregoing remarks, because I do not believe there is any drug capaable of destroying adult filariæ in the human system. Surgeon-Major E. Laurie, of Hyderabad, reports two cases which he believed to have been promptly cured by thymol,[1] the maximum dose being five grains twice daily. Walsh, of the general hospital of Calcutta, also reports success from the use of thymol. On the other hand, Crombie, of the same institution, has given two hundred grains of thymol daily in one case, and forty-five grains daily in another, without producing any effect upon the worms. As the latter justly remarks, "thymol is so exceedingly insoluble that it is improbable that any appreciable quantity of it left the intestinal canal."[2]

I consider it a very fortunate circumstance that the case of Fanny B. came under my observation at a time when I was able to secure the co-operation of such an expert in photomicrography as Dr. Charles Lester Leonard, whose arduous work has been pursued in the Laboratory of Hygiene of the University of Pennsylvania. The appended illustrations are all *photographs of the living parasite*, and this is, I believe, the first time in which the living filaria has been photographed under a one-twelfth oil-immersion lens, or, so far as I am aware, under any. The representations are, therefore, absolutely accurate, and necessarily take precedence of any drawings of the living or photographs of the dead nematode. To show the fallacy of drawings I may say that one artist pictured the worm with long cilia waving from its head, while another was unable to see anything of the sort in the same specimen. I may say, in this connection, that I am inclined to believe in the existence of such cilia, although they are not shown in the photographs; unless they are indicated by the blur in Fig. 5. The point I wish to emphasize is that nothing can be represented in the photographs that was not present at the time they were taken.

I may say also that I have been unable to detect the "cephalic armature" described by Manson, although the "pouting" movement

[1] Lancet, February 14, 1891. [2] Ibid., August 13, 1892.

of the head was plainly visible. In mentioning my inability to detect the cephalic spine, or fang, I have no intention to impugn the accuracy of Manson's description. I attribute my failure entirely to my deficient training in this line of research.

In conclusion, I wish to express my thanks to Dr. Anna M. Fullerton, the distinguished physician in charge of the Woman's Hospital of Philadelphia, and to her assistants, Drs. Blackburn and Carpenter, for their kind and skilful co-operation with me in my study of this interesting case.

POSTSCRIPT. I visited Fanny B. at her home on March 25th, and found her in good condition. She informed me that since leaving the hospital her baby's feces have been stained blue. She is taking ten grains of methylene blue daily—two grains every three hours.

March 28th. Patient's milk now faintly stained blue. Treatment continued.

29th. Visited the patient this evening and prepared eleven slides, in every one of which I found filariæ in most active movement. She has now been taking methylene blue since March 12th. From the 12th until the 21st, the dose was two grains every three hours—sixteen grains per diem—and from the 21st until the 29th it has been ten grains a day, in divided doses of two grains. The drug, in this case, has proved absolutely inert. The patient's urine is deeply stained, and her milk very slightly stained. The baby's fecal discharges are blue, and his urine also of a faint-bluish tint. Filariæ of a very faint-bluish tinge. Leucocytes unstained. A few filaments of cotton on the different slides were stained of a faint-bluish tint by the blood-plasma with which they were in contact.

From the above it is manifested that my experience with methylene blue in parasitic chyluria is entirely different from that of Austin Flint and Joseph N. Henry.[1]

The latter in his report to Flint says:

> The effects of methylene blue in this case were decided and prompt. After the administration of two grains every two hours during the day on March 5th, the parasites were very few at 11 P.M.; the only two found were deeply stained with blue, and their movements were extremely sluggish, the urine being clear, but intensely blue. On the fourth and seventh days no parasites were found, although the treatment had been discontinued after the first day.

[1] New York Medical Journal, June 15, 1895.

FIG. 1.

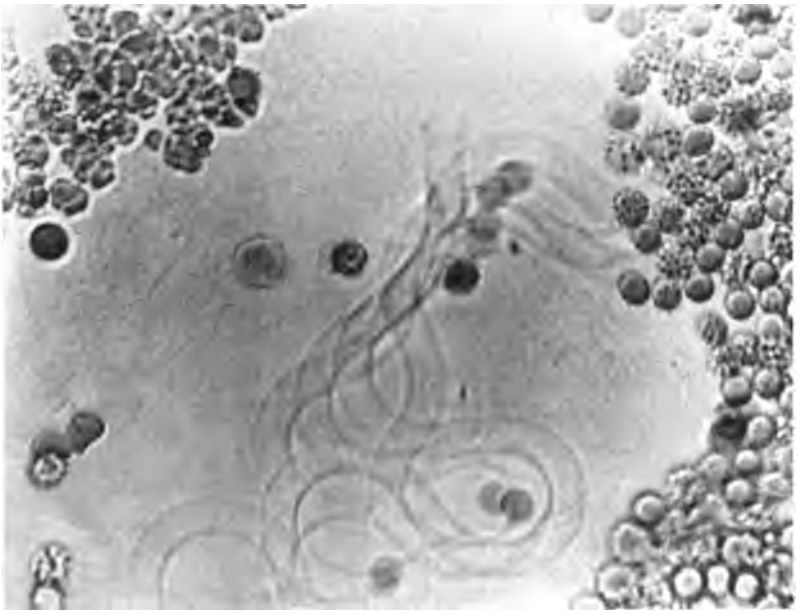


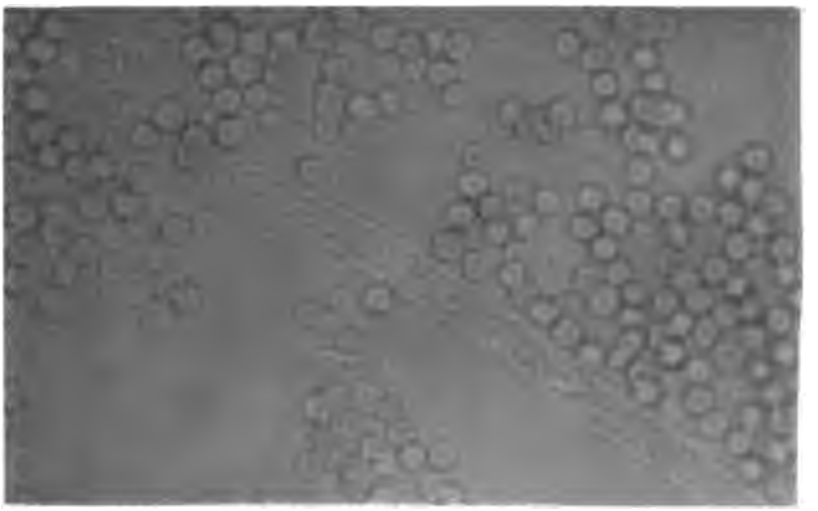
FIG. 2.

FIG. 3.

FIG. 4.

Fig. 5.

Fig. 6.



On the eighth day the urine became milky, and on the night of the ninth day filariæ were found in great number, but their movements were not very active. On the tenth day the treatment was resumed and continued for five days. Three days after, the blood being examined at night, a very few motionless filariæ were observed. Since that time and up to the present writing the urine has been normal and the patient has been restored to perfect health.

Admitting the disappearance of the parasites in Joseph N. Henry's case, I believe it to have been a mere coincidence and in no way related to the administration of methylene blue. I have given this drug in larger doses than were used in the case reported by Flint, and for a much longer period, without the slightest effect upon the parasite.

EXPLANATION OF THE PLATES.

FIG. 1. The movement of a single filaria during a series of four successive instantaneous exposures. The length of each exposure was one-fifth of a second, the entire series occupying less than five seconds. The magnification is to eight hundred diameters, with a Zeiss one-twelfth homogeneous immersion lens.

FIG. 2. Filaria alive in the blood. Instantaneous photomicrograph. Four hundred diameters magnification. Four millimetres Zeiss apochromatic.

FIG. 3. The same as Figure 2. Magnified to fifteen hundred diameters. Showing structure and commencing granular degeneration.

FIG. 4. Tail of filaria showing sheath extending beyond the apparent end of the tail. Eight hundred diameters.

FIG. 5. Head of living filaria. The blur in front of the head is probably due to the motion of cilia. Fifteen hundred diameters.

FIG. 6. Shows the head of a filaria overlapping a red corpuscle. The appearance might readily be mistaken for the cephalic end of a sheath. Magnified eight hundred diameters.

DISCUSSION.

DR. ANDREW H. SMITH: In the early part of the past winter a patient was admitted into the Presbyterian Hospital, New York, in my service, with a history extending back from five to ten years of having filaria, contracted in South America. He presented the elephantiasis, legs enormously distended, lymph scrotum, and there was a history of chyluria. He had had a large abscess in the calf of one of the legs and the cicatrix was deeply depressed, showing that a decided loss of substance had taken place. He had been able to go about for a number of years, but in a crippled condition, owing to his enlarged leg, but not suffering particularly except on occasions. About five times in the history of his disease he had had acute attacks of fever, persisting a number of days. His fever ran high, and it was on account of one of such of these attacks that he sought admission to the hospital. We found numerous parasites, but they were found as readily in the daytime as in the night, and they were all dead. We never succeeded in finding a living one. He remained with us for several months, and had a second one of these febrile attacks, from which he recovered in a degree, but he left us finally with the same condition as when he first came. I would observe also that at one time these parasites were found in the serum which exuded from punctures in the legs.

DR. THEOBALD SMITH: In the use of methylene-blue it should be remembered that this substance is reducible, and when it comes in contact with living organisms like bacteria or living tissue it becomes decolorized, and if the leucocytes are alive the supposition would be that the methylene-blue would not stain them. Either the methylene-blue is not absorbed by living cells or it passes into them and is reduced to a colorless substance. The dead substance will be colored, whereas living organisms, like embryos of parasites, should remain unstained if alive.

S. J. MELTZER: I would like to ask Dr. Henry why he expects, if the patient dies, that an abscess will be formed.

DR. HENRY: I believe that an abscess would be formed because abscesses often form under such circumstances; at least, adult filariæ have been removed from abscesses in various parts of the extremities. In one case an East Indian surgeon opened a lymphatic abscess, as he called it, in the inner aspect of the arm, and removed six or more adult filariæ, and this experience has been repeated in a number of cases. The parent worm is two or three inches long, and is plainly visible to the unaided eye. It has been compared to an animated hair. If such a parasite perishes in the body, its decomposition, one would suppose, might very readily give rise to an abscess.

With reference to the report of Dr. Smith's case, the filariæ were found during the day; were they found during the night also?

DR. A. H. SMITH: At all times, and always dead.

DR. HENRY: If it was constantly present in the superficial vessels it belonged to the variety of filaria which is found on the west coast of Africa, the *filaria Perstans*. This parasite is found in negroes and in whites who have visited the Calabar region, on the west coast of Africa. Possibly the parasites in Dr. Smith's case were killed by the manipulations of the slides. I had to caution those who withdrew the blood for me against pressing the cover-glass down upon the blood. If that is done, the filariæ are certainly killed. In some of the slides I have here there are dead filariæ near the edge of the cover-glass where the blood is thick and coagulated. If even gentle pressure is made, they are apt to be destroyed, although their power of resistance to cold and heat and such like influences is enormous.

In Dr. Smith's case the presence of fever is interesting. Sir Joseph Fayrer has described this form of fever accompanying elephantiasis where there are large growing glands, lymph scrotum, and other manifestations of filariasis, giving it the title of elephantoid fever. It is markedly intermittent in character, so much so that many of the filarial manifestations, especially orchitis, have been ascribed to malarial influences. I recall a paper on malarial orchitis reported by Dr. Gregorio Fedeli, of Rome. While I have been studying this subject of filariasis the question has arisen in my mind whether this so-called malarial orchitis which Fedeli has described as prevalent in Italy may not have been filarial orchitis.

Dr. Smith's case is interesting because the parasites were found not only in the elephantoid tissue, but also in the blood. In elephantiasis the parasites frequently are absent in the blood because of the damming up in the groins and in the inguinal regions. In cases of elephantiasis the adult is in the extremity. The adult female pours forth swarms of embryos, some of them immature, which block up the groin glands and bar the way to their passage into the blood by way of the thoracic duct.

As to methylene-blue and its mode of staining I would say that I did not use it with any object of ascertaining whether it stained or not, but merely to determine whether it exerted any deleterious influence upon the parasites. I will here again reiterate and emphasize the fact that the parasite should be treated kindly. As Manson says, the host who harbors such a guest as the filaria should treat it kindly. Otherwise the female worm, if irritated, will abort. The products of such abortion are globular, and instead of being about $\frac{1}{8500}$ of an inch in diameter are about $\frac{1}{750}$ of an inch, and cannot traverse the lymphatic glands, and will give rise by obstruction to chyluria and other symptoms. As long as the female does not abort and the filariæ come to temporary perfection, they are innocuous. I may say here that chyluria is a rather rare manifestation of filariasis. Manson says he seldom sees it.

NOTES ON THE TREATMENT OF PERNICIOUS AND OTHER FORMS OF ESSENTIAL ANÆMIA.

By I. N. DANFORTH, M.D.,
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THE following notes are written chiefly for the purpose of inviting discussion and eliciting information. They are based upon the continuous observation of a single case of pernicious anæmia. This diagnosis was the concurrent judgment of Marie J. Mergler, H. M. Lyman, Frank S. Johnson, James B. Herrick, A. H. Foster, and myself. Other questions presented themselves, such as the possibility of malignant disease of the liver, spleen, or pelvic organs, degenerative nephritis, or malarial poisoning, but they were all eliminated by repeated and careful examinations. On two or three occasions some bodies were found in the blood which bore some resemblance to the malarial plasmodium, but they were not characteristic, and quinine produced no effect upon them. Moreover, the case presented a typical history of pernicious anæmia from its beginning, about 1891, to its fatal end in August, 1895. The patient was a female, aged fifty-two years at the time of her death; married; had borne two children in natural labor, both now living and in vigorous health; she came of a healthy and long-lived English ancestry, without any traceable hereditary tendency to disease. There was no post-mortem examination.

Iron was most faithfully tried. On several occasions it was well-borne and did good service, but only for a time. Almost invariably after a few weeks' trial the symptoms of gastric irritation became so pronounced that the remedy had to be discontinued. As the symptoms of gastric irritation disappeared after the iron was suspended and returned when it was resumed, there could be no doubt as to their cause, especially as this same experience occurred again and again. The same thing happened when the preparation of peptonate and albu-

minate of iron were tried; in fact, neither of these much-vaunted preparations was as tolerable as the ferric citrate. Iron-by-hydrogen in small doses—not more than a grain three times a day—was borne without any gastric trouble, and it could be given—in fact *was* given, continuously for weeks together. It produced very slight blackening of the dejections, which was regarded as evidence of its absorption and assimilation, but, on the other hand, no beneficial results were apparent, either as to general increase of strength or increase of blood globules or hæmoglobin. In all forms, chalybeates seemed quite inert, so far as any hæmogenetic powers were concerned, while they were sources of irritation to the gastro-intestinal tract, with the single exception mentioned. It is a question worth considering, whether the iron found in the liver in pernicious anæmia is not derived from that which is ingested in the form of "tonics," as indicated by the researches of Jacobi, Gottlieb, and others. The acid preparations of phosphorus were used with temporary benefit. The most efficient, as well as the most agreeable, was the proprietary preparation known as "Horsford's acid phosphate," which is a solution of the phosphate of lime, magnesia, and potassa, with an excess of free phosphoric acid. On two different occasions a remarkable and rapid gain followed the use of this preparation, but it was only temporary. Preparations of hyposulphites were not only useless but harmful, on account of resulting gastric irritation. As the compounds of phosphorus seemed theoretically indicated, several of them were patiently and persistently tried; but the results were either entirely negative or positively injurious, on account of the gastro-intestinal disturbance which followed. But in the case on which these remarks are chiefly founded, as well as in several other cases of profound anæmia, I have seen prompt and decided benefit follow the use of the acid preparation of phosphates already mentioned.

Intestinal antiseptics, of which β-naphthol should, in my estimation, be regarded as the best type, were of considerable temporary service when there were decided indications of gastro-intestinal fermentation, attended by flatulent distention of the abdomen. Being stimulated thereto by the experiences of Gibson and Hunter, and their somewhat overdrawn deductions, I was anxious to make a thorough trial of intestinal antiseptics, and had considerable hope of favorable results. But the outcome was negative or disappointing, except that when

decided gastro-intestinal disturbances, as indicated by flatulent distention, pain, nausea, and diarrhœa, were present, beta-naphthol was quite efficient in the relief of these symptoms; not more so, however, than dermatol, salol, or benzosol; and neither one of these was well borne for any length of time, on account of gastric irritation produced by the remedy itself. In short, as regards the cure of pernicious anæmia, or the restoration of the lost blood-making power, intestinal antisepsis proved perfectly useless. Alcoholic stimulants, that is, distilled liquors, were absolutely valueless, except as transitory or "diffusible" stimulants in times of emergency, such as fainting from heart weakness, respiratory exhaustion, or vertigo. They were taken unwillingly, were likely to be followed by nausea, headache, and loss of appetite, and it was found advisable to employ them as little as possible. The malt liquors, such as export beer, stout, and ale, were very much better borne and proved real aids to digestion. Of the varieties named, the export beer produced the best results, undoubtedly because it contained diastase in considerable quantity. In fact, it aided digestion and improved the appetite far more than the preparations of pepsin, or, indeed, any other remedies given with that end in view.

Since arsenic was prominently brought into notice by Byrom Bramwell as a remedy in essential anæmia it has attracted widespread attention, and much evidence of its usefulness and efficiency has been accumulated. I have not however found a well-authenticated case of permanent cure of pernicious anæmia as a result of arsenical treatment. Many cases of substantial improvement are recorded; in a considerable number relapses have occurred, and in none which I have come across has sufficient time elapsed to warrant the assumption that a permanent cure has been accomplished. Moreover, in not a few of the published cases, I think the diagnosis may be fairly questioned, while in some the question of doubt amounts to a certainty. In my case arsenic seemed to be of little positive or permanent value. It was faithfully tried in the form of Fowler's solution uncombined with other remedies. Not more than seven or eight drops could be given at a dose, and much of the time the maximum dose was five drops, given three times a day—that is, from fifteen to twenty-four drops per diem as a maximum amount. The larger doses advocated by many practitioners were simply impossible in the case in question. Nausea, vomiting, eructation, gastro-enteralgia, anorexia, and diarrhœa inva-

riably followed every attempt at giving the remedy in anything like efficient doses. Other preparations were tried with no better results, combinations with other remedies were made, and, in truth, many faithful and persistent attempts were made to adapt arsenic to the peculiarities of that particular case, since we physicians all realized the paramount necessity for its employment; but we found it impossible to use it in doses larger than five drops of Fowler's solution, or its equivalent in other forms, for any length of time.

The "Levico" water formed a possible exception to other forms of arsenic as regards toleration, and some benefit was believed to have been derived from its use. This water was not obtained until late in the history of the case, too late, undoubtedly, for any remedy to have accomplished any decisive results. It was well borne by the stomach, did not occasion any indication of gastro-intestinal irritation, and some temporary improvement seemed to follow its use. In other forms of anæmia I have since used it as an adjunct to other tonic remedies, and have had reason to regard it as a hæmogenetic. The Levico water is represented to be an "arsenio-ferric" natural water, derived from a spring, or two springs, situated in the town of Levico in the Tyrol. It has a strong styptic, metallic taste, a specific gravity of 1.003, feebly acid reaction, and when evaporated leaves a brownish-red deposit. I have not been able to find any analysis giving its exact constituents. I have been very favorably impressed regarding it, however, and propose giving it further trial.

In the month of April, 1894, my attention was arrested by a brief account of Frazer's case of pernicious anæmia, treated successfully by bone-marrow. I lost no time in administering the remedy in the case under consideration. I first adopted Frazer's plan of giving the yellow marrow; it was administered in capsules, in the form of sandwiches, dissolved or suspended in bouillon, and by other methods devised by the ingenuity of the nurse. In less than a week an unmistakable improvement in the patient's condition had taken place. The appetite was restored, the slight pyrexia disappeared, and an accession of strength was noticeable. Meantime, believing that the marrow of cancellated tissue—the red marrow—ought to be the most potent as a hæmogenetic, I set about preparing a glycerin extract thereof, but it was a fortnight before the preparation was ready for use. During this fortnight, however, the patient steadfastly gained,

and the result was manifestly due to the yellow marrow, which had been administered three or four times a day. But it had become repugnant to the patient, and I should have been compelled to suspend it in a few days longer. At this juncture I began using the glycerin extract of red marrow, made by contusing the sternal end of calves' ribs and macerating them in glycerin for eight or ten days. At first the glycerin extract was given pure, except that it was diluted with a little water. Later it was combined with Fowler's solution of arsenic and Horsford's Acid Phosphate, each dose containing two drachms of the glycerin extract of marrow, five minims of arsenical solution, and twenty minims of acid phosphate; and this dose was given three times a day. Under this treatment a steady and progressive improvement took place, so that early in May the patient left her bed and joined the family at table, soon after she was riding out, and in June—two months after beginning the marrow treatment—she left Chicago for a summer residence in the country, still continuing the marrow extract. Early in the autumn of 1894 she returned to her home vastly improved in physical strength, with hæmoglobin increased from 30 to 80 per cent. and the red globules normal in number and appearance. In November the marrow extract was dropped, the patient having wearied of incessant dosing. Her health continued fairly good until the Christmas holidays, when she experienced a severe and sudden relapse, which was attributed to the exactions of the holiday season. The bone-marrow was at once resumed, and it again asserted its power, the patient slowly regaining a fair degree of health, so that in March, 1895, she was out of doors and able to superintend her household affairs. She continued to gain until the last of April, 1895, when another relapse occurred, for which no adequate reason could be given. From that time forward the bone-marrow utterly lost its power, and all other remedies were equally useless. The case rapidly manifested the malign symptoms so graphically described by Addison, and death occurred August 1st, purely from the exhaustion of anæmia.

As I recall the history of the case, with its alternating periods of hope and despair, I cannot resist the conclusion that the patient's life was prolonged for nearly eighteen months largely, if not wholly, by the bone-marrow. By this I do not mean to exclude or minimize the effects of the concentrated food and other tonics which were em-

ployed, but I do mean to assert that the bone marrow accomplished more than all these put together, and that without the aid of this death would have occurred in April, 1894, instead of August, 1895. It is useless to attribute the gain to the arsenic instead of the bone-marrow, because, first, arsenic was faithfully tried before the bone-marrow was given at all, and it failed, probably because it could not be given in adequate doses; secondly, because manifest improvement took place in the patient's condition under the use of bone-marrow without arsenic, as I have already stated; and, thirdly, because it was never given in doses larger than five minims three times a day—a quantity altogether too small to account for the marked improvement witnessed. And yet in spite of the obvious and gratifying results which followed the use of the bone-marrow, the blood-making power was not restored to the patient, and she did not recover.

There is quite too much probability of the correctness of the position of Prof. Lionel Beale when he says that "the cases of pernicious anæmia which recover are not pernicious anæmia at all."

During the progress of the case which I have related I was called to see a very intelligent physician in an advanced stage of "pseudo-leukæmia." The symptoms were typical; there was general enlargement of the lymph-glands, the patient was confined to his bed, hæmic murmurs were present, his weakness was extreme, and I expected death in a few days. But I did what I was expected to do—prescribed extract of bone-marrow. Four or five weeks later this patient almost paralyzed me by walking into my office. He attributed his wonderful gain entirely to the bone-marrow, which had been taken continuously, a statement in which his wife, a very intelligent lady, entirely concurred. Indeed, both the doctor and his wife were extravagant in their praise of bone-marrow, and the doctor regarded himself as well on the road to recovery. About two months later still I was called to see the doctor again. He had lost all he had gained, and was near his end. After a few weeks of such marked improvement that it was regarded as almost miraculous, the bone-marrow lost its power, and the fatal end came only too rapidly.

In many cases of simple uncomplicated anæmia I have seen excellent results from the administration of bone-marrow. I do not, however, claim that it possesses any marked superiority over iron or arsenic in such cases; perhaps it is no better than the older hæmogenetics; time

must determine that question; but it is sometimes available when neither iron nor arsenic can be taken, and then it adds a new and efficient remedy to our armamentarium. As regards the form of bone-marrow, I think the glycerin extract of the red marrow best adapted for practical use and most efficient as a hæmogenetic.

DISCUSSION.

DR. ANDREW H. SMITH: This paper reminds me of a case which was under my care at the Presbyterian Hospital, New York City, about two years ago, in which the diagnosis was between pernicious anæmia and carcinoma of the stomach. The patient came in with a great degree of anæmia and complete anorexia. There was no tumor present, or vomiting or pain. Examination of the blood showed that there was no deformity of the corpuscles, and the ratio between the white and red corpuscles was preserved, although the degree of anæmia was very great, the number of red-blood corpuscles being below 1,000,000 in the cubic millimetre. An examination of the stomach contents showed an absence of free hydrochloric acid, and on one occasion some lactic acid apparently was present. There were elements therefore looking in both the direction of carcinoma and of pernicious anæmia present in this case. The patient was placed upon iron and arsenic, but there was a continual decline of strength until he was unable to stand on his feet. The iron and arsenic were abandoned under the belief that the case was not one of pernicious anæmia, and shortly afterward, with no apparent cause, there was a most amazing improvement in the condition of the patient. His appetite returned and he was able to get up and help about the ward, and was finally discharged from the hospital at his own request. If the case had passed out of observation at that stage we might have thought that it was a case of pernicious anæmia which was relieved by the treatment which had been instituted, although the relief was not apparent until after the cessation of treatment. I was, however, enabled to trace his history afterward, and I found that he returned to his home in New England, and after a period of apparently approximate recovery he declined again and died. At the autopsy cancer of the stomach was discovered.

DR. JANEWAY: I think that anyone who has made observations upon the treatment of any one of the three diseases, leukæmia, pseudo-lukæmia, and pernicious anæmia, must have been struck by the frequency with which at times marked improvement happens, so much so that not a few of the cases in literature reported as cures of these diseases have come from observations during one of the temporary improvements. In regard to leukæmia, I have seen marked temporary improvement in treatment, but I have yet to see a case where a cure has been permanent. The only case which I have

had where it was asserted that a cure was obtained was treated by arsenic, iron, and hæmoglobin, the hæmoglobin being freshly obtained from ox-blood, which was defibrinated and the hæmoglobin separated by alternate freezing and thawing. This case was the only one in which I could get a physician to carry out the treatment fully. In that case the doctor wrote me that a cure had finally been effected. The white corpuscles had been diminished and the spleen had become reduced to the proper size. He wanted to publish the case two years ago, but I told him to wait. I shall write to him and ask what has been the subsequent course in the case. With this exception case after case, some with marked temporary improvement, have gone on to fatal issue. The same is true of pseudo-leukæmia. Sometimes the glands will go down remarkably under arsenic, and cases reported cured in two instances by previous observers have come under my observation in a relapse, and then the arsenic and iron failed to give any amelioration and they went on to a fatal termination.

Dr. Hunn has told me of a case of pernicious anæmia which I had seen and placed upon bone-marrow, and under this treatment, under his observation, improvement, has continued.

I must confess that the treatment of these conditions with any of the methods with the hope of producing permanent cure is to my mind illusive, provided that the condition has been correctly diagnosticated.

One word about the diagnosis of leukæmia, for I have seen so many mistakes by very competent observers that I think it is a point worth mentioning, and that is, that men often fail to examine the blood in patients with enlarged spleens, because the patient with leukæmia does not show enough pallor to make the physician believe that he is dealing with this complaint. The diminished number of red blood-globules would undoubtedly cause pallor in the patient with simple anæmia; but it fails to show in this disease. The opacity of the blood, owing to the white globules, is great, and the lips have a dirty-red color rather than a peculiar pallor. I noticed this years ago in my first case—because that had gone through the hands of five very good physicians—because of the absence of pallor without recognition.

DR. F. P. HENRY: I called attention many years ago to the fact that marked pallor was not common in leukæmia,[1] and I thought it was generally known; in fact, hæmatologists recognize a condition of leukæmic plethora. That is a striking point of distinction between leukæmia and pernicious anæmia.

With reference to reporting cases cured I think that at least two years should elapse before one should venture to do so. I have under my care a gentleman who has been cured of pernicious anæmia for the space of two years by the use of arsenic pushed to the point of tolerance. There is no use in giving arsenic in small doses; it must be pushed to the point of tolerance, and sometimes when so pushed it will cause bronze discoloration of

[1] See Treatise on Anæmia. P. Blakiston, Son & Co., Philadelphia, 1887, page 87.

the skin. The gentleman I have mentioned had all the signs of pernicious anæmia, but has recovered and is now an active business man in Philadelphia.

I may say here in reference to Dr. Janeway's case, in which arsenic and hæmoglobin were given simultaneously, that under such a line of treatment I would attribute the success to the arsenic, which is of all drugs the one most to be relied upon.

DR. J. P. CROZER GRIFFITH: It seems to me that the reason the cases are so hard to cure is that no one yet has been able to reach the real cause of the trouble. I have no reason to change the views which I expressed before this Association some years ago on the pathology of the disease, following the observations of Hunter, that pernicious anæmia is really a hæmolysis, a destruction of the red blood-corpuscles in the portal circulation particularly. One can see therefore why there should be no benefit from iron. There is usually already more hæmoglobin present than corpuscles in pernicious anæmia, showing that there is some hæmoglobin free in the circulation. What we want to do is to make corpuscles and then supply them with hæmoglobin. Bone-marrow and arsenic are often able to do this; but when they are removed or their action ceases, a relapse of the disease occurs. I have noticed in some recent reports of the use of arsenic in pernicious anæmia that, although the number of red blood-cells was increasing favorably, the percentage of hæmoglobin still kept ahead of the corpuscles. This showed conclusively that although corpuscles were being formed rapidly an abnormal hæmolysis was still going on. If the disease ceases under the administration of arsenic, it is because, for some reason not understood and independent of the drug, the destruction of blood has ceased. When we find what this destruction of blood is due to and how to reach it, then we can cure pernicious anæmia. It is very probable, however, that the cause of this blood destruction is very different in different cases. It would certainly seem to be the absorption of some poisonous material from the digestive tract. Viewed in this way the cases of extreme anæmia which have attended atrophy of the gastric mucous membranes or the presence of bothriocephalus latus are to be called pernicious anæmia and are due to the absorption of some toxic material.

DR. JANEWAY: I used the hæmoglobin with the idea of supplying two things, probably a ferment as well as the iron. I thought in that way something in the blood that might act as a stimulant could be introduced.

DR. M. H. FUSSELL: A case came to the out-patient department of the University of Pennsylvania in the spring of 1892 with general anasarca, extreme anæmia, great dyspnœa, and hæmic murmurs over the heart. We viewed the case as in all probability one of nephritis. However, repeated examination of the urine showed it to be entirely normal, and blood examination showed the red corpuscles at about 1,500,000. He was put on ascend-

ing doses of arsenic and recovered practically. His blood-count came up to 4,000,000 and the hæmoglobin to 75 per cent. We lost sight of him until the spring of 1893, when he returned in very much the same condition as at his first visit. We again put him on ascending doses of arsenic, and he this time took the dose of sixty drops of Fowler's solution daily for quite a long time. This sixty drops finally caused a furious neuritis. The case improved again and he went back to his work as a roller in a rolling-mill. In the spring of 1894 he again returned with a worse condition than the first time. Again on arsenic he improved. I saw him only a few days ago, and made the following notes: "April 16th, two years after his last attack, is a very large, portly fellow, florid, weighs 250 pounds; hæmoglobin 90 per cent. and blood corpuscles 4,800,000." Curiously enough he does not complain of anything. His urine has been examined innumerable times and always found normal until now, when it contains 5 per cent. of sugar. I attribute this probably to the fact that his occupation has been changed from that of a roller in an iron-mill to watchman. He is a large consumer of starches, and in all probability this is a glycosuria simply.

DR. HARE: Within the last two years I have seen several cases which apparently were true pernicious anæmia. What interested me particularly about these cases was that the pernicious anæmia very evidently arose from different causes. I had two patients in the hospital at the same time in bed alongside one another, one of whom improved wonderfully under ascending doses of arsenic, while the other died in a few weeks under the same treatment.

I have now under my care a boy presenting many of the symptoms of pernicious anæmia who has been the rounds of all the large hospitals of Philadelphia, who has had since he entered the Jefferson Hospital several exacerbations in which we thought he would die. He developed the dyspnœa and all the symptoms of distress due to the profound dyscrasia in the blood of quite advanced cases. He tells us that during his residence in the Episcopal Hospital on three occasions the physicians thought he would die. Eventually he took seventeen drops of Fowler's solution three times daily and made a wonderful improvement under this treatment, so that I thought that permanent improvement might result. As soon as he reached this dose, however, his stomach rebelled and he suffered another relapse, which was as severe as any he had previously had. He himself thought at this time that he "would die for sure." For some time after the arsenic was stopped the boy had practically no treatment at all, and a period of improvement occurred, thus illustrating the fact that these cases of pernicious anæmia very frequently improve rapidly with no treatment.

The fact of the matter is that until we can find out something more definite about the pathology of the disease we cannot base any therapeutic measures on rational grounds.

IDIOPATHIC OSTEOPSATHYROSIS (FRAGILITAS OSSIUM) IN INFANCY AND CHILDHOOD.

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EXCEPT in old persons fragilitas ossium, or osteopsathyrosis, as it was first called by Lobstein (*Traité d'Anatom. Patholog.*, 1833, T. ii. 204), is a condition comparatively so uncommon that it receives but little attention from most writers of text-books, and that instances of it are always of interest. Even special articles of value upon the subject are few in number. The most exhaustive and satisfactory is the classical contribution by Gurlt (*Handbuch der Knochenbrüche*, 1862, Theil. ii., 147), which contains a number of cases cited from medical literature. Among other writers Volkmann (Pitha-Billroth: *Handb. d. allg. u. spec. Chirurg.*, 1865, B. ii., Abt. ii., Hlft. i. 365) gives a short but very useful review of the subject. Enderlen (*Arch. f. pathol. Anat.*, 1893, cxxxi. 223) collects a few cases additional to those of Gurlt, and the article by Linck (*Arch. f. Gynecol.*, 1887, xxx. 264) is of value. More recently Schultze (*Arch. f. klin. Chirurg.*, 1894, xlvii. 327) and Moreau (*Contribution a l'étude de la fragilité des os*, Paris, 1894) have written regarding it, limiting themselves largely to the idiopathic form. Simon (*Des fractures spontanées*, Paris, 1886) and Dubrueil (*Etude oritique sur les fractures spontanées*, Paris, 1891) have discussed it in theses upon spontaneous fractures.

Several varieties of osteopsathyrosis may be distinguished. Thus we may have it either symptomatic to other affections or occurring idiopathically—*i. e.*, not associated with any discoverable cause. The symptomatic forms depend upon various conditions. For instance, rachitis is capable in many instances of occasioning actual transverse fracture, as well as great bending of the bones. Osteomalacia likewise

may produce fractures, and sometimes to such an extent that an *osteomalasia fracturosa* (Kilian) has been described. Cases of fragilitas due to scurvy have also been reported, and it is possible that some of the instances of brittleness in infants may be attributable to it. Syphilis has long been considered a cause of osteopsathyrosis. It is a disputed point whether congenital syphilis may occasion a general brittleness of the whole osseous system, depending upon some unrecognizable change in the structure of the bone, or whether the fractures are always the result of localized gummatous processes. The studies of cases by Gangolphe (*Malad. infec. et parasit. des os*, 1894) failed to show any cases of fragility of bone in congenital syphilis independent of local lesions, and Volkmann believes that syphilitic fractures are the result of a gummatous osteitis. There certainly seem to be good grounds for believing that at least most of the cases of fragilitas attributed to the general effect of syphilis are so attributed without good reason. Simon believes that both hereditary syphilis and scorbutus are more apt to occasion separation of the epiphyses.

There are, further, a whole series of causes which probably produce atrophy of the bone and consequent fragility. Many of these are of a distinctly nervous nature. Thus we find fragility sometimes developing in locomotor ataxia, poliomyelitis, and mental diseases. There are also atrophic changes resulting from simple inactivity, and those commonly attending old age. There is some question, however, whether the fractures which so often and so easily occur in old persons depend always on fragilitas, whether they are not in many cases brought about by the diminished power old persons have of guarding themselves against falls and other accidents capable of producing fractures.

Finally, there is a series of local causes for fragilitas, among them osteomyelitis, carcinoma or other malignant growth of the bone, gummata, echinococcus or other cysts, and localized necrosis.

It is, however, only with idiopathic osteopsathyrosis that we have to do in this connection, and, to narrow it still more, only with those cases in which the disease begins in infancy or childhood. The following case is a remarkable instance of the very early, almost congenital presence of the disease. I saw the child with Dr. B. H. Detwiler, of Williamsport, Pa., to whom I am indebted for the facts of the clinical history:

H. E., male, aged two years and ten months. The family history is good, both parents and grandparents being unusually healthy people. The only exception is that a brother of the mother had never been able to walk, and died at the age of six years. His affection, however, seems to have been rather a mental one than any involvement of the bones. A brother of the patient died when five months old, apparently through the effect of heat. The patient, who is the second and only other child, was born July 11, 1893. Labor was not protracted nor severe. Nothing unusual was noticed until the second day after birth, when it was found that the right thigh was fractured, and, on further examination under an anæsthetic, the left thigh was also found to be broken in the neck. Both limbs were placed in long splints and dressed with a silicate of soda bandage. In three weeks the dressings were removed and union was found complete. On September 11th, at the age of three months, the right humerus and right femur were broken. The accident appears to have been the result of a medical examination, since the boy cried as though in pain while it was going on. As the examination was made with due gentleness this shows the exceeding brittleness of the bones. Both bones united nicely. On March 1; 1894, he was sitting in his chair, lost his balance and fell forward, but not out of the chair, producing a fracture of the right femur near the hip. On September 11, 1894, just a year after the former accident, he broke his left thigh again. Union took place, but in October, two weeks after the dressings had been removed, the bone was fractured again. This time it was kept in splints four or five weeks. When examined during anæsthesia the femora appeared to be abnormally thin In the spring of 1895 he fell out of his hammock and broke both his thighs. Union took place well. Three months later he broke his right thigh.

Besides these fractures there were times when he appeared to be having pain in various parts of the body, supposed to be rheumatic, but which was undoubtedly due to undiscovered fractures, since at least one fracture of the left thigh and one of the right forearm, both of which united with angular union, were found afterward. On several occasions he has broken his ribs. It is estimated that he has had in all 17 or 18 fractures, and he certainly has had 12. The fractures have always been attended by pain, but do not appear to have been preceded by it. Union has always been prompt. The child was nursed until the age of five months. After that he was fed with cow's milk and later with nourishment suitable to his age. The general health and nutrition are good. The appetite is good, and there have been but slight digestive disturbances. He is carried constantly upon a stretcher, lest sitting him up should produce fractures.

I saw him for the first time December 3, 1895. Examination was difficult, owing to the great terror which the child had of doctors, and the danger of fracture which handling entailed. He was a plump, apparently well-developed and healthy-looking boy, lying comfortably on his back on a stretcher. The head was decidedly larger than normal. The frontal bones had distinct bosses suggesting rickets, and the back of the head was flattened, doubtless

from the long-continued pressure caused by the enforced position. There were no other evidences of possible rickets connected with it. The chest was of normal shape and there was no bending of the ribs. There were no enlargements of the epiphyses of the long bones. The right arm had a bad angular deformity shortly above the wrist and the left thigh was similarly deformed at the upper third, with eversion of the foot. Curvature of the bones in any part of the body could not be detected. The muscles of the calves were well developed, but the thighs were flabby. The arms were well developed. He had been taking cod-liver oil for some time. I advised that he be carefully accustomed to sit up in order to give his muscles the needed exercise.

I saw him for the second time in April, 1896. He had improved greatly. He could now turn himself over and move his legs freely, and could sit upright in the lap, although he still needed support. The muscles were evidently gaining strength rapidly. His general condition was excellent. His head, however, seemed even larger than at the first examination, although not hydrocephalic in appearance nor of rickety shape. It seemed, in fact, simply to be an unusually large head for his size. There had now been no fractures since the preceding summer, and the fragility seemed evidently less. I advised the use of phosphorus in addition to the cod-liver oil, and that he have plenty of fresh air and all the exercise he could be made to take with safety to his limbs. I could not obtain a specimen of urine.

I have looked somewhat extensively through medical literature in search of cases of idiopathic osteopsathyrosis in childhood, in the effort to learn what light the experience of others might throw upon the cause, nature, and treatment of this strange affection. There have been but few cases reported with a degree of brittleness greater than, or even as great as, that shown by the case just detailed; and even instances with a less, although still decided, brittleness, with the occurrence of multiple fractures, have not been common. The list which follows, which is not claimed to be a complete one, is the result of the search. Cases have been excluded in which the disease appeared to have commenced after puberty, and most of those also in which but one or two bones were fractured apparently from slight causes. Those cases, too, have been omitted in which it seemed certain from the other symptoms or from the post-mortem examination that the undoubted fragility was secondary to some other disease. Instances of multiple intrauterine fracture, in which it seemed likely that accidents happening during pregnancy were sufficient to account for the lesions, have also been rejected. On the other hand, a number of doubtful cases have been included, although with explanatory remarks

to that effect. The observations are not arranged in any alphabetical or chronological order.

A. CASES SHOWING DIRECT INHERITANCE.

The influence of inheritance has been very marked in a number of instances, the disease having appeared in the parents or grandparents, and perhaps affecting several children of the family. The following cases represent this direct inheritance:

I. Greenish (*Brit. Med. Journ.*, 1880, i. 967). In a family the grandfather, A, had been an invalid on account of multiple fractures. He had three sons and two daughters. The daughters and one son had no fractures, but of the remaining two sons one, B, had suffered 1 fracture, and of his children one son had 13 fractures by the age of nineteen years, the first break occurring when very young. Most of the fractures healed promptly, but some were very slow. Another son had 2 fractures, the result of a severe accident. One other son and two daughters escaped accident. A's other son, C, had 2 fractures, and of his children one son had 8 fractures, one son 3, three sons each 4, and one daughter 3 fractures. Four other daughters escaped accident. The cause of the fractures was usually slight.

II. Pauli (*Untersuch. u. Erfahrung. im Gebiete der Chir.*, 1844, 35. Quoted in *Dublin Hosp. Gaz.*, February 1, 1846, 189). The members of a family otherwise healthy had all had fractures; three of them had each 2, one 3, and one 5 fractures. No considerable violence was required. No fracture occurred before the age of eight years. All healed with unusual rapidity. A second break never took place in the seat of a former one. Both the father and grandfather had been liable to fractures.

III. Willard (*Med. News*, 1887, ii. 734). The father and mother showed no evidence of syphilis and denied having had it. The children were small, puny, and had notched teeth, and some were almost dwarfs. The father had 3 fractures, all from direct violence. One daughter, eighteen years old, had 9 fractures by the age of twelve years, the first occurring at twelve months. One daughter had 5 fractures by the age of sixteen years, the first at four years. One daughter, aged eighteen years, had 3 fractures by the age of twenty-two months, but none since. The first was at eight weeks. One son had 4 fractures by the age of eight years, the first being at two years. One daughter fractured her left clavicle at birth, during an easy labor, and fractured it again at thirteen months. One daughter fractured her right clavicle at the age of one week. One daughter fractured the left clavicle at the age of three weeks. One son fractured a rib at seven years of age. A grandchild, the child of one of the affected daughters, broke its thigh at the age of four weeks, and broke it again at nine months.

Nearly always the fractures resulted from some insignificant cause. Union

was usually speedy. In the femora the fractures were nearly always in the line of the callus.

In this case the presence of fragility in the father is doubtful, but its inheritance by the grandchild is undoubted.

The following instance of fragility is so interesting on account of the remarkable inheritance that I include it, although there is strong doubt upon the propriety of calling the osteopsathyrosis idiopathic:

IV. Ekmann (*Dissertatio medica descriptionem et casus aliquot osteomalaciæ sistens.* Upsaliæ, 1788. Quoted by Gurlt, *loc. cit.*, 148). The great-grandfather, A, had limbs so deformed that he could not walk. In the next generation one son, B 1, lost all strength in the arms and legs at the time of puberty. One daughter, B 2, was small and deformed and waddled. One son, B 3, was a dwarf and had a decided bend of the arms and legs. In the third generation —the children of B 3—there was one son, C 1, who experienced fractures from the slightest causes from earliest infancy. His limbs were bent and he was unable to walk. In the fourth generation—the children of C 1—one son, D 1, when scarcely a month old, had his arms and legs so soft that they bent with the slightest touch, and later fractured three or four times in every year of his childhood. One daughter, D 2, had a fracture when eight days old, without the action of any discoverable force, and later, during childhood, suffered fractures from the slightest causes.

It would seem that the ancestor of this family was deformed, but whether from bending or breaking is not stated. The next generation showed softening of bone apparently without fracture. The next showed remarkable fragility which seemed far to exceed the softening. The last generation exhibited great softening with fragility in one case, and seemingly fragility only in the other.

V. Goddard (personal communication to Gibson. *Instit. and Pract. of Surgery*, 1850, 8th ed., i. 236). A boy of thirteen years had had 14 fractures, all from very slight causes, and all healing promptly; 4 of them occurred by the age of four years. His mother had had 6 fractures and her brother 13 (11 in thighs and 2 in arms) up to the age of thirteen years.

VI. Hamilton (Case reported by Armenag Assadoorian. *Physician and Pharmacist*, February, 1870). A man of fifty-three years broke the left elbow when a child, and two years later the right elbow. No union took place. Some time later he broke the left clavicle. In all he had 11 fractures and 2 dislocations. With regard to one accident it is stated that union was slow. His father broke both forearms at the elbow. Two paternal uncles each broke a leg and one of them an arm. A sister had one fracture, and she or another sister had another. A brother had 5 fractures and 1 dislocation.

VII. Graham (*Bost. Med. and Surg. Journ.*, 1884, cx. 467). A man [it would seem of thirty-two or thirty-three years of age] had his first fracture at eighteen months. He continued to have them at frequent intervals, and had in all 18 fractures by the age of eighteen years, but none since. His father had 14 fractures, and a cousin of his father's 21. The father's paternal uncle also was a bone-breaker:

VIII. Cox (*Eclect. Med. Journ.*, Cincinnati, 1879, xxxix. 458). A girl of eighteen years had never been able to walk [presumably from early fractures]. Her lower extremities were greatly deformed and she had had in all 7 fractures, 5 of them of the femur. The brother of thirteen years had never been able to walk [but it is not stated whether there had been fractures]. The father and several of his brothers had bones easily broken.

IX. Hiester (*Boston Med. and Surg. Journ.*, 1849, xli. 393). A well-developed girl of sixteen years fractured her leg in going upstairs. This was her 3d fracture. [The age when the others occurred is not stated.] Three other children of the family had had 8, 7, and 3 fractures, respectively. The maternal grandfather had 4 or 5 fractures.

X. Battles (personal communication to Gross. *System of Surgery*, 1882, 6th ed., vol. i. 871). Of eleven children five, all males, had fragility of the bones. One of them, aged twenty-four years, had 64 fractures; the next had 34; the third child, aged thirteen years, had 30; the fourth, aged eleven years, had 10; the fifth, aged two years, had 2. All were situated in the thighs, occurred usually from slight causes, and united promptly. No severe pain was experienced. The six daughters resembled the father in appearance, but the five sons looked like the mother, through whom the fragility seemed to be inherited; her father and several of her brothers and sisters having brittleness of the bones.

The following instance is a doubtful one, since the "fractures" may have been but separations of the epiphyses:

XI. Atherton (*Dominion Med. Monthly*, 1894, ii. 1). A boy of thirteen years fractured his olecranon twice on each side, making 4 fractures in all. There was a tendency in the family to fractures from slight causes. The paternal grandfather had 3 or 4 fractures, and the paternal grandmother very frequent fractures. The father had at least 6 fractures, and the paternal uncles had broken their bones. The patient had two sisters, both of whom escaped.

B. CASES SHOWING A FAMILY PREDISPOSITION.

There are other cases than those detailed in which no direct inheritance is reported, yet in which there is a striking family history, more than one child being the subject of the disease, or perhaps other relatives suffering from it. The cases of this nature which I have been able to find are as follows:

XII. Pritchard (*Lancet*, 1883, ii. 394). A male child, apparently healthy, fractured both humerus and femur without history of accident two days after birth; on the next day broke the other humerus through being moved in bed; and in three weeks broke the other femur. All united promptly. The father was one of eight children, two of whom had fractures in infancy. The only brother of the father had four children, three of whom had fractures apparently spontaneously soon after birth.

The case reported by Pritchard shows a remarkable degree of indirect inheritance. It is not stated that the fathers themselves suffered fractures.

XIII. Axmann (*Ann. f. d. ges. Heilk.*, 1831, iv. 58. Quoted by Gurlt, *loc. cit.*, 149). The writer gives his own family history. He and his two brothers were of rather delicate build. He had a fracture of the leg in his third year; one brother had 9 fractures from the age of two to that of nineteen years, 4 of them occurring before six years of age. The other brother had 9 fractures from the age of two to that of nineteen years, 4 of them before he was five years old. These 14 fractures occurred without the action of noteworthy force. All healed in four or five weeks. The fragility decreased with growth and disappeared at maturity.

This case is doubtless the same as that referred to by Lobstein (*loc. cit.*) and reported by Strack (*Neues Journ. d. pract. Arzneyk. u. Wundarzneyk.*, 1806, xxv., 3 St., 163), and, according to Gurlt, is probably the same as that described by Renard (*Versuch. ü. die Entstehüng u. Ernährung des Knochen*, Leipzig, 1803). I have not been able to obtain the original. It seems very possible, too, identical with that reported by Mebes, and presently to be detailed. (XVIII.)

XIV. Arnott (*London Med. Gazette*, 1833, xii. 366). A girl of fourteen years, a patient at the Middlesex Hospital, suffered her first fracture at the age of three years and had in all 31 fractures, viz., thighs 13, legs 10, arms 7, forearm 1. Slight falls, or even turning around suddenly, were sufficient to cause them. Union was always complete and remarkably prompt. A sister of six years had 9 fractures, the first at eight months. The general health of both girls was excellent. Two brothers and one sister were unaffected.

XV. Agnew (*Princip. and Pract. of Surgery*, 1878, vol. i. 918). A child of three years with a fracture of the thigh had broken the same bone the year before. Five other children in the family had each had fractures of some part of the skeleton; two of them each 3 times, and one, an infant of three weeks, having had a rib broken by being turned in the nurse's arms. The author believes that a syphilitic taint in the father was the cause of the fragility. [However, no evidences of the existence of syphilis in the children are mentioned.]

XVI. Moreau (*Contribution a l' étude de la fragilité constitutionelle des os.* Thèse de Paris, 1894). A girl, aged twelve years, broke her leg at the age of five years, and had 7 fractures within four years and ten months. All but one were in the legs. Her sister, aged nine years, broke her leg at the age of five years, and had 10 fractures within two years and eight months. All but two were in the legs. All the fractures in these two cases were produced by insignificant causes and all healed promptly. The children were apparently healthy, without history of syphilis or rickets. The father died of progressive paralysis. The mother had by her first husband two children unaffected by the disease.

XVII. Jones (*Medical Archives*, St. Louis, 1866, iii. 127). A man of twenty-four years, of excellent general health. At the age of three years he broke both legs as the result of a slight fall. Since then there had been numerous fractures, about 50 in all, chiefly in the lower extremities. The slightest fall would be sufficient to cause them. Little pain attended and union was rapid. Great deformity finally resulted, making the patient unable to walk. A cousin, the niece of his father, had been afflicted in a similar manner, and had numerous fractures.

XVIII. Mebes (*Die Knochenbrüche, etc.*, 1845, 35). This writer states that among other instances of the affection he knows of a family where three children had broken legs and arms 8 times within five years.

This brief note corresponds so closely in the number of cases and in the age with the account given by Strack (*loc. cit.*) of the early history of the Axmann family (see XIII), that it seems very possible that the cases are identical.

C. ISOLATED CASES.

There are a considerable number of cases reported in which no history is given of inheritance of the malady or of family predisposition. I have been able to find the following instances:

XIX. Blanchard (*Chicago Med. Journ. and Exam.*, 1876, xxxiii. 7. Later and more completely in *Transac. Amer. Orthop. Assoc.*, 1893, vi. 83). A woman, aged twenty-seven years, experienced her first fracture at the age of two months. Up to the age of nine years, when first reported, she had had 41 fractures. At twenty-seven years she was unable to walk and had had about 106 fractures. Her own weight was sufficient to break her legs, and she frequently had produced fractures by turning in bed. Not much inflammation or pain attended them and no pain preceded. Union was remarkably tedious, for when dressings were removed at the end of the second or third month the bone was still pliable, and angular bending would begin and continue until more than a year after the accident. Great deformity finally ensued.

XX. Blanchard. (Case of Frankenthal.) (*Transac. Amer. Orthop. Assoc.*, 1895, viii. 275.) A woman of twenty-nine years, who commenced to have fractures in the second year of life. Up to the time when reported she had 17 fractures of the long bones and 2 dislocations. There was but slight pain or inflammation with the accidents. Union was very tedious. At the end of two or three months it was not firmer than rubber, and two or three years passed before it was completely firm. Dressings were usually removed after two or three months, and angular curvature then commenced and increased until the end of one or two years.

XXI. Blanchard (*ibid.*). A girl of four years fractured her right femur when two years old, by falling from a chair. It was neglected and angular deformity resulted. About six months later she broke her left femur through a very slight fall, and again in six months broke it in another place. Union was prompt and perfect in the last two fractures.

XXII. Fleming (*Edinb. Med. Journ.*, 1862, viii. 24). A man of twenty-four years had his first fracture, the thigh, when eighteen months old, and since then had in all 53 fractures, viz., thighs 35, ribs 8, forearms 5, jaw 1, fingers 4. The simplest causes were sufficient. Union was remarkably prompt in the fracture under observation—the last one.

XXIII. Gibson (*Instit. and Pract. of Surgery*, 1850, 8th ed., vol. i. 234). A man of twenty-two years, previously of excellent health, had extraordinary brittleness of the bones from infancy, and had suffered in all 24 fractures from the slightest causes, such as tripping over a rug, walking, etc. Union was prompt and without much deformity.

XXIV. Velpeau (*Gaz. des Hôpitaux*, 1847, 2 ser., ix. 265). A girl of excellent general health had her first fracture at the age of fourteen months, and before the age of fifteen years had had 6 fractures—thigh 5, arm 1. All resulted from very slight causes, twice while merely walking. The last fracture united slowly. She had also had 3 dislocations.

XXV. Earle (quoted by Stanley, *Diseases of the Bones*, 1849, 195). A boy of ten years had 8 fractures—6 in one tibia and 2 in one femur—each in a different part of the bone from the preceding ones. All united within the usual time.

XXVI. Mettauer (personal communication to Gibson, *Institutes and Practice of Surgery*, 1850, 8th ed., vol. i. 235). A man of seventy years had been subject to fractures from earliest infancy. The tendency to fracture had seemed to increase with age. The slightest cause was sufficient, such as mounting a horse, a sudden twist of the body, etc. Recovery was always astonishingly speedy.

XXVII. Corson (*The Clinic*, Cincinnati, 1873, iv. 157). A well-developed infant cried for five hours after a difficult birth. On the eleventh day a fracture of the thigh was discovered and nine days later the other thigh was fractured; two days later still the humerus broke, and at this time callus was discovered on the radius and ulna.

XXVIII. Langton (*Brit. Med. Journ.*, 1895, ii. 1234). A girl had been by

the age of eleven years the subject of several spontaneous fractures as the result of muscular action or very slight injury. All united but one, which had been roughly treated. In this one union was never firm. Subsequently two fractures which had been firm parted again, and in one of them a sarcoma developed by the age of twenty-three years.

XXIX. Houston (*Dublin Journ. Med. and Chem. Sciences*, 1836, viii. 474). A well-developed boy of five years had his first fracture at three years. Within two years he broke each tibia and each femur once. The cause was always inconsiderable, and the fractures occurred twice while running. Union was always prompt.

XXX. Schultze (*Arch. f. klin. Chirurg.*, 1894, xlvii. 327). A girl, thirteen years old, was weak when born, but later grew well and strong. She had her first fracture, the right femur, at nine months. At one and a half years of age the same place broke again. Up to six years of age she had 5 more fractures without any trace of bending, and by her thirteenth year she had had not less than 30, viz., right thigh 7, left thigh 5, right leg 6, left leg 4, right arm 2, left arm 4, right forearm 2. All were produced by the slightest causes. Pain was nearly absent in fractures of the upper extremity, but present in those of the lower. Union took place in a shorter time than in normal bone. Great bending and twisting of the lower extremities finally developed. Operation showed the tibiæ to be much flattened, and with the marrow cavity of the right tibia scarcely visible and no trace of it in the left. The right tibia and fibula were united by a flattened exostosis.

XXXI. Linck (*Archiv. f. Gynäcol.*, 1887, xxx. 264). No history of accident to or disease of the mother. Labor was easy. A premature child which died shortly after birth. There were fresh fractures and old healed and unhealed fractures of all the ribs—40 on the left side and 44 on the right—which had caused numerous nodules and bendings; 10 fractures of the extremities—6 of them fresh—and united and recent fractures of the clavicles. No enlargement of the epiphyses or of the junction of the ribs and cartilages was anywhere found. The microscopical examination showed the bones to be practically normal.

XXXII. Parker (*New York Med. Journ.*, 1852, n. s., ix. 96). A girl of eleven years, previously in poor health, had her first fracture—of the tibia—at the age of six years. Five months later she broke her right thigh, and when about ten years old her clavicle. The cause was always insignificant, and union was always prompt.

XXXIII. Howell (*Atlanta Med. and Surg. Journ.*, 1884, xxv. 82). A healthy man of twenty-eight years had his first fracture—the left thigh—in his second year, through falling from a chair. A few years later he broke the right thigh. By the age of twelve years he had broken his right thigh 3 times and his left thigh 2 times, and a year or two later he broke his left thigh again. The 7th fracture was of the right thigh in his sixteenth year, and the last fracture was of the left thigh at twenty-eight years. The last united slowly.

The following cases are even more briefly described by those reporting them than are some of the last:

XXXIV. Tamplin (*Lectures on the Nature and Treatment of Deformities*, 1846, 234). A girl of seventeen years, of unhealthy appearance and pallid, had had about 40 fractures produced by walking or other slight causes. [The age when the disease began is not stated.]

XXXV. Dawson. According to Corson (*The Clinic*, Cincinnati, 1873, iv. 157) W. W. Dawson "presented at one of his clinics" a child of three years who had suffered more than a score of fractures. The readiness with which the bones united was one of the most prominent features.

XXXVI. Willett (*Brit. Med. Journ.*, 1895, ii. 1235) states that he remembered a child who had broken 6 of its long bones, only one of the fractures showing any signs of callus.

XXXVII. Ridd (*Schmidt's Jahrbücher*, Jahrg., 1868, Bd. ii. 631). [This is the reference given by Linck, but I have not succeeded in verifying it, and there seems to be some mistake in it.] A healthy mother had a premature child which lived nine days and died suddenly in a convulsion. The autopsy revealed 54 fractures, partly recent, partly united by callus.

XXXVIII. Ketch (*Trans. Amer. Orthop. Assoc.*, 1893, vi. 86) saw a child some years ago in a public clinic in New York who would have a fracture on turning in bed. [I have been unable to learn anything further about this case.]

XXXIX. Hoadley (*Trans. Amer. Orthop. Assoc.*, 1893, vi. 85) says that Bond showed a case of fragilitas twenty years ago in the Chicago Medical College. The child [sex not stated] was about twelve years old, and there had been about 119 fractures. The bones are said to have been soft in the earlier stages. The fractures united with great facility. [I have been unable to discover where the case was first reported.]

XL. D'Outrepont (*Abhandlungen u. Beiträge geburtshülflichen*, Inhalts. Th. 1. Bamberg u. Würzburg, 1822, 228; quoted by Gurlt, *loc. cit.*, 225). A stillborn child exhibited signs of fracture of the right thigh, both upper arms, and the left clavicle. Callus, which seemed probably to be recently formed, was found on the bones at the autopsy.

XLI. D'Outrepont (*ibid.*, 233; quoted by Gurlt, *ibid.*, 225). A child, after an easy labor, was found to have fractures of the left femur, right humerus, right clavicle, and two ribs. No cause was discovered. The child recovered.

XLII. Wight (*Annals of Surgery*, 1893, xviii. 662). A boy of eighteen years had great deformity of the legs and thighs from angular union of fractures. The father stated that his son had always been subject to poor health, and that he had had fits, and that this was the cause of the crooked bones. [Apparently the deformity was the result of frequent fractures of the fragile bones caused by muscular action during the fits. The age when the convulsions began is not stated.]

D. ISOLATED CASES WITH SOME ELEMENT OF DOUBT.

The following instances of the disease, occurring in a single individual of a family, have some element of doubt attached to them as regards their belonging strictly to the class of idiopathic osteopsathyrosis. In some of them the writers mention the existence of rickets, although it is not convincing in every instance that this disease had been present; for the older writers, and many more recent ones as well, were disposed to attribute all cases of early fragilitas to rickets as a matter of course. In other cases rickets certainly had existed at one time, but the fragilitas showed itself at a time when rickets must have ceased to be active. It does not seem at all clear that the two conditions were at all interdependent in these cases.

In other instances we have to do with cases which resembled in some particulars the so-called fœtal rickets, but in which there was a degree of fragility by no means corresponding with that usually seen in this condition. Finally, we have certain intrauterine cases where the fractured or membranous condition of the bones of the cranium, or the very great number of fractures occurring widespread in fœtal life, lead to the suspicion that the cause may have been an insufficient advancement of the ossifying process. Such a condition is, however, a very obscure one, and does not satisfactorily explain the fragility. I have, therefore, provisionally included these causes with the others as instances of idiopathic osteopsathyrosis. Although there is a history of accident to the mother during pregnancy mentioned in some instances, it does not seem sufficient in the cases I have selected to account for the fractures.

XLIII. Jacquinelle (*Journ. de Méd., Chirurg., Pharm., etc.*, 1788, lxxvii. 267, and 1790, lxxxiv. 216). A man of thirty-two years undoubtedly had rickets severely as an infant, and could not walk until five years old. He was then fairly well until twelve years old, when he had his first fracture, one of the arm. He had a fracture of both thighs at fifteen years, and one of the arm two years later. In all he had 6 fractures. The degree of force required was inconsiderable. Union was prompt and complete.

XLIV. Lonsdale (*A Practical Treatise on Fractures*, 1838, 21). A girl in whom there had been 22 fractures from the most trivial causes. Most of the bones were rickety. Union took place in the usual time. [The age of the girl is not stated, nor is the evidence of rickets explained. From the context it appears that there was no bending of the bones in this case.]

XLV. Barwell (*Brit. Med. Journ.*, 1882, ii. 1155). A girl of seventeen years, with great bending and deformity of the bones of the extremities, but with no bending of the ribs nor enlargement of the epiphyses. Between the ages of nine and thirteen years she broke her arm 4 times and her ribs on several occasions. He describes the case as rhachitic osteomalacia, stating that it was neither rickets nor osteomalacia. [The late development and the absence of positive signs of rickets make it probable that this is an instance of idiopathic osteopsathyrosis.]

XLVI. Lange (Günsburg's *Zeitsch. f. klin. Medizin.*, 1852, iii. 263). A girl of eleven years, of scrofulous habitus and with pigeon breast, had in all 6 fractures. Two years later she had her 7th fracture. [Nothing is said as to the age when the first fracture occurred, nor is there anything to suggest rickets unless it is the pigeon breast.]

XLVII. Esquirol (quoted by Malgaigne, *A Treatise on Fractures*, Amer. ed., 33) had in his collection the skeleton of a rhachitic female in which nearly all the long bones were broken, and more than 200 fractures could be counted. [Nothing is said of the age, but it is safe to presume that with such numerous fractures the disease must have been present in childhood, and that something more than rickets was present.]

XLVIII. Malgaigne (*A Treatise on Fractures*, Amer. ed., 33) says that in the Musée Dupuytren is a skeleton of a child, of six or seven years, with general rachitis and with 12 fractures.

XLIX. Malgaigne (*ibid*, 31). A boy of ten years, who had been badly rachitic in early infancy and whose legs and arms were distorted by the disease. His first fracture occurred at the age of six years, and he had 4 by ten years. No special force was required. All healed well.

L. Chaussier (*Bull. de la Fac. de Méd. de Paris*, 1814, iii. 306). A female child, dying twenty-four hours after an easy labor. The long bones of the extremities were shorter and thicker than normal and more or less curved. There were found 113 complete fractures, some of them united, some still yielding to bending and with crepitation, and with the periosteum in these places much thickened. The ribs alone had 70 fractures.

LI. Barker (*Brit. Med. Journ.*, 1857, ii. 806, 823). A female child, dying ten minutes after birth, which had not been difficult. The mother had repeatedly had falls on a flight of stone steps. The examination of the child showed an entire absence of bone in the covering of the brain, and numerous fractures of both the upper and lower extremities. The bones were remarkably brittle, the merest pressure snapping the ribs like glass. Chemical examination of the bones showed too small a proportion of inorganic material—33.34 p. c. The writer believes that arrest of development did not account for the fragility, since the fractures were situated where ossification had advanced the most.

LII. Hirschfeld (*Gaz. des Hôpitaux*, 1857, 291). A seven-months' male fœtus, born dead. The mother had had a fall. The fœtus showed no evidence of rickets. The vault of the skull seemed made only of minute thin plates

of bone. The long bones of the extremities, the ribs, and the clavicles exhibited a number of fractures, certainly over 20.

LIII. Vrolik (*Tabulæ ad illustrandam embryogenesin hominis et mammalium*, 1849, Fol. Tab. 91, Fig. 1, 2; quoted by Linck, *loc. cit.*). A child which died three days after birth. The parents had been syphilitic, but the mother bore an entirely healthy child the next year. The skull was hydrocephalic, and, when skeletonized, was found to consist largely of a great number of irregular pieces of bone, suggesting Wormian bones. The extremities and the ribs exhibited numerous fractures, some fresh, some united by callus.

LIV. Dupuytren (*Bull. de la Fac. de Méd. de Paris*, 1811, ii. 154). A little girl, very delicate, and with a weakly mother. At the age of two months she had her first fracture—the arm—without known cause, and two months later she broke the left thigh while lying down. At eight months of age she broke the right thigh; this last was preceded by a curvature of the limb. At two years and four months the right thigh appeared to be giving way, and after some days it broke as the result of a fall. Then the earlier of the old fractures softened and the bones became bent.

LV. Dubrueil (*Étude critique sur les fractures spontanées*, Paris, 1891). A boy of ten years, of a healthy father but rhachitic mother, had his legs bent in infancy by rhachitis. He suffered his first fracture—the humerus—at six years, and had 4 fractures by the age of ten years. The cause was slight in all; there was not much pain, and union was not delayed.

LVI. Cecconi (*Giornale dell. soc. med. chir. di Parma;* quoted in Hufeland's *Journ. der pract. Arzneyk*, 1816, xlii. St. 4, 124). A child dying seven hours after an easy birth. All the epiphyses had been broken "in the direction of their length." The shoulder-blades were the only ones spared. Crepitation could be heard and felt. No history of accident to the mother. [It is not clear from the description whether or not this is an instance of separation of the epiphyses, but it would seem not. I have not been able to obtain the Italian original.]

LVII. Schroeder (*Medicin. Zeitung d. Verein f. Heilk. in Pr.*, 1843, 136). A girl of five years, of rhachitic constitution and the subject of a tapeworm, broke both thighs in an attack of convulsions. She had had the same accident three times in the two preceding years.

LVIII. Volckamer (*Miscellanea curiosa med.-phys.* Acad. N. C., Dec. 1. Ann. 2, 1671, Obs. 225, p. 327; quoted by Gurlt, *loc. cit.*, 230). A boy of ten years, the subject of epilepsy since three years old. A few months before death he broke his tibia and humerus in a violent convulsion, and shortly after this experienced more fractures. The autopsy showed still more fractures that had not been recognized.

In these last two cases the fractures were evidently the result of violent muscular contraction, but there must probably have existed fragility as well.

Chaussier (*loc. cit.*) quotes certain cases of intrauterine fractures

cited by older writers which seem to be instances of remarkable fragility; but whether these were due to true osteopsathyrosis or to some lack of development cannot be surmised from the nature of the reports. Moreover, as he remarks, there is reason to doubt their existence, since the reports are founded largely upon hearsay. The cases are those of Malbranche, Hartzoeker, and Muys, as follows:

LIX. Malbranche (*Traité de la recherche de la vérité*, liv. 2, chap. 7). A young man, an imbecile, whose body was broken in the same places in which the bones of criminals are broken. He had lived more than twenty years in this state. Maternal impression, from seeing the punishment of criminals on the wheel, was assigned as the cause.

LX. Hartzoeker (*suite des Conjectures Physiques*, Amsterdam, 1708). A woman who lived to the age of thirty-two or three years, always confined to bed, with her bones everywhere broken as in the case of criminals. Assigned to maternal impression, as in the last case.

LXI. Muys (in the preface to *De musculorum artificiosa fabrica*, 1751). A child born at term to a woman who had seen an execution upon the wheel. The child had all its members broken like those of a thief.

LXII. Notta (*Bull. Soc. Anat. de Paris*, 1849, xxiv. 83). A male child of a healthy mother. The head at birth was remarkably soft and could be compressed like a vessel of water. The child died soon after birth. The autopsy showed ossification but little advanced, and much of the bone of the skull made of numbers of small irregularly shaped pieces about 1 cm. in diameter, and separated from each other by membranous tissue. The bones of the trunk were normal, the tibiæ, femora, and bones of the left forearm were somewhat curved, and the ends of the radii swollen. The bones of the extremities presented 15 fractures, 12 of which were recent, 2 consolidated, and 1 uniting.

LXIII. Harvey (*Med. Herald*, St. Joseph, 1891, x. 255). A boy in whom at birth the whole vault of the cranium was nearly without support or protection. There were double bowleg and anterior curvature [which may have been the result of intrauterine fractures]. When three days old he broke the left arm, and by the age of two and a half months he had 8 fractures. Severe falls had accounted for some of them. [For the others the cause is not stated.] Crepitus was very evident in all fractures. The child grew and looked well.

LXIV. Schmidt (*Monatssch. f. Geburtsk. u. Frauenkr.*, 1859, xiv. 426). A weakly child of healthy parents died shortly after an easy birth. All the bones seemed to crepitate when the body was handled, and were entirely broken, each in two or three places. The head felt like a broken egg. The autopsy showed the bones of the lower extremities three or four times broken; some of the fractures already united, some with slight callus, and some with none. The bones broke or pressed in with the slightest force. The bones of the head were composed of numerous small bony plates. Microscopic examination by E. Wagner led to the conclusion that the condition was a con-

genital non-syphilitic atrophy of the entire skeleton, best described as a chronic parenchymatous osteitis; quite different from osteomalacia or rachitis or the ordinary osteitis.

LXV. Baudelocque (case described by Marc in *Dict. de Sci. Méd.*, 1816, xvi. 64). Labor was rapid and easy, and there had been no violence done to the child, which died a few days after birth. The autopsy showed 43 fractures of the long bones, including most of the ribs. Even some of the cranial bones were broken. Some of the fractures were consolidated and others were in process of union.

This is the same as a case reported by Chaussier (Proces verbal, etc.—see *loc. cit.*, 306).

LXVI. Amand (*Nouveau obs. sur la prat. des acc.*, p. 92, obs. viii. Quoted in *Dict. des Dict. de la Méd. Francaise et Etranger*, 1840, iii. 219). A fœtus of four or five months. The bones were separate and movable in the middle of the forearms, thighs, and legs, and seemed joined only by the skin.

LVII. Griffith (case now reported).

A short review of the affection, based upon these reported cases, is in place here.

Etiology. As the name idiopathic implies, we find that the histories of the cases collected throw little light upon the cause of the disease. The influence of *heredity* is the only point which strikes us forcibly, inasmuch as direct inheritance, or at least a family tendency, was shown in 18 of the 67 reports. This influence of inheritance is so marked that Gurlt has compared the affection to hæmophilia and Moreau to progressive muscular dystrophy. There is a distinct difference in the line of inheritance, the influence of the male greatly predominating. We notice, namely, that in the 11 families in which direct inheritance (from parent or grandparent) obtained the disease was transmitted in 7 instances from the father, and often from the grandfather as well, and that in 2 more instances, Hiester's and Battles', it descended through an unaffected mother from an affected grandfather. Of the 2 remaining families, in 1, Willard's, the disease appears to have been transmitted from the father, and was certainly so from one of his affected daughters to her children, while in the other, Goddard's, it was the mother who was subject to fractures. In Atherton's case, although the transmission was predominantly by the males, the grandmother as well as the grandfather was subject to fractures.

In the matter of the etiological influence of *sex*, the accounts are not sufficiently accurate to allow of any reliable figures being given, since in many cases the sex of the children is not stated. It is noticeable that of all the cases, young and old, occurring in the family connection of the 18 observations where inheritance or family tendency to the disease was marked—if we leave out the instances reported by Ekmann as too anomalous—at least 47 were males and but about 19 females, with 24 whose sex is not mentioned. This shows a tendency to a transmission not only through males but to males. Of the total number of cases developing in childhood here reported there are, as nearly as can be counted, 41 males and 32 females; but there are so many others whose sex is not stated that no conclusion can properly be drawn.

As to the *age*, there is a decided tendency for the affection to begin early in life. There are a number of cases reported which began later, yet the abstracts here given, although limited to the disease as seen in childhood, still contain a large proportion of the instances of idiopathic osteopsathyrosis reported for all periods of life. This list does not, of course, contain instances of the secondary forms, which include the atrophic fragilitas of old age. Details are not complete enough to allow of more than general statements, but we find that in many instances fractures occurred before birth, in still more they appeared a little later, and in a few the fragility developed only as growth advanced, notably in the cases of Pauli.

It is worthy of note that the amount of *force* required to produce fractures was nearly always very slight, and sometimes remarkably so. Among the causes mentioned are going upstairs, leaning over, turning around, being moved in bed, tripping, turning in bed, the slightest fall, and the like. In Blanchard's first case the mere weight of the body was sufficient to break the legs, and in my own case the thighs were fractured on one occasion by the child falling forward while in a sitting position.

The influence of *other diseases* in producing idiopathic osteopsathyrosis is problematical. In some cases the children have been weakly, but as a rule this was not the case. The influence of syphilis seems to have been practically negative in the cases I have collected. Were it otherwise they could not be included in the category of an idiopathic condition. The mere fact that a parent was, or was supposed to be,

syphilitic is not sufficient to explain the strange fragility. I have, as stated already, excluded from this list those cases in which it seemed reasonable to believe that the tendency to fracture might be the result of the presence of multiple gummata of the bones. So, also, there seems to be no good reason to attribute a special fragility to the coexistence or previous existence of rickets. Rickets is an extremely common disease, yet fragilitas, such as the abstracts exemplify, is rare. Then, too, fragilitas so often appears at an age when rickets has not yet developed, or sometimes comes on when rickets has ceased to be active. It has been claimed that a previous rickets produces later a condition of fragilitas, but this is an assumption for which I have been unable to find any adequate proof.

Pathology and Pathological Anatomy. This is, if possible, even less understood than is it setiology. The relationship of osteopsathyrosis to osteomalacia and to rachitis is a question which forces itself upon us. It is evident that the process differs entirely from osteomalacia. In this latter affection there is an increasing softness of bone with a remarkable tendency to bending and to absorption of the inorganic material. Fractures, if they occur, are purely of a secondary nature, for the prime factor is the softening. The family reported by Ekmann is a pointed instance of a combination of osteomalacia and osteopsathyrosis, or, rather, of the appearance of the two diseases singly or combined in different members of the same family. It is not a proof of their unity.

Rachitis is much more closely allied to osteomalacia than to osteopsathyrosis. There is in children a natural tendency to infraction of bone—*i. e.*, to the occurrence of green-stick fractures; and in rachitis this tendency is greatly exaggerated. In osteopsathyrosis, on the other hand, just the reverse of this is seen, and the condition is one of extreme brittleness without disposition to bend. Rachitis, as has already been pointed out, sometimes causes true fractures, but far oftener does not. When, therefore, we find an excessive degree of fragility in a case of rickets it is rather an evidence that rickets and osteopsathyrosis may be combined in the same individual—not a proof that they are at all identical or even necessarily related. It must, too, be borne in mind constantly that in many cases in which curvature of the limbs is spoken of the condition may very possibly have been the result of fracture and not of bending.

Cases of the so-called fœtal rickets have been described repeatedly. The pathological position of this condition is not certain. Orth (*Path. Anat. Diagnost.*, 1894, 681) claims that it has nothing whatever to do with rickets. Some of the reported cases exhibit a remarkable softness of the skull, with great fragility of the bones of the extremities, yet without any of the characteristic symptoms of rickets. Cases of this nature I have provisionally placed in the category of osteopsathyrosis, since they seem to belong there better than elsewhere.

But few chemical and microscopical examinations of the bones have been possible, and these have made the matter but little clearer. In the case reported by Linck the microscopical examination showed that the calcification of the projecting portions (the callus) at the seat of fracture was not perfectly developed, but that the bone elsewhere was normal. In Schultze's case excised pieces of tibia showed the marrow cavity nearly obliterated in the right leg and quite so in the left. But as this was at the seat of former fracture it taught little. The bones in Barker's case, which is one of the possible instances of imperfect ossification, gave on chemical analysis 33.34 per cent. of inorganic matter, and 66.66 per cent. of organic matter, thus showing a great deficiency in the amount of the former. On the other hand, in a typical case of idiopathic osteopsathyrosis occurring in an adult and reported by Enderlen (*Archiv. f. path Anat.*, 1893, cxxxi. 223) there was in the portion of femur examined an excess of organic material of only 6.27 per cent.—a figure wholly inconsiderable. Finally, in the case of Schmidt, which was one of the doubtful cases similar to that of Barker, the microscopical examination indicated the presence of a chronic parenchymatous osteitis, which Wagner called a "non-syphilitic atrophy." These are all the examinations which have been made among the cases collected here. As may be noticed, they are contradictory; and, if we leave out the doubtful cases and take only the more typical ones of Linck and Schultze, and the adult case of Enderlen, we find no change present which accounts in the slightest degree for the fragility.

Gurlt suggests that a certain compactness in the bone, rather than any alteration in the chemical composition, explains the fragility, and Ziegler, as quoted by Schultze, suggests some pathological alteration of the basis of the framework of the bone. Moreau believes that there

is some nervous basis for the disease, and that a lesion of the anterior horns of the spinal cord is the most probable cause.

Verneuil (Virchow-Hirsch, *Jahresbericht etc.*, 1885, ii. 317) examined the urine in three cases of spontaneous fracture, and found it remarkably rich in phosphatic salts, and Blanchard reported a large amount of earthy phosphates in the urine of his first patient. It is possible that this may have some bearing upon the pathology of the disease, but further studies are needed.

An interesting feature of the affection is that in nearly all cases union of the broken bones was prompt, and generally remarkably so. Sometimes the fragments united so readily that, as in Mettauer's case and in the one which I had under observation, professional advice was often not even sought for. This rapidity of union has been pointed out by many writers. The most noteworthy exceptions which I have discovered were Blanchard's first and second cases, where union was extremely tedious. Some of the fractures in Velpeau's, Hamilton's, Howell's, and one of Greenish's cases united slowly, and some remained ununited in the cases of Langton, Hamilton, and possibly Willett.

With regard, again, to the cases of very numerous intrauterine fractures, and especially those with soft and crepitating cranii, for whose origin the assumption of an imperfect ossification has been made, it is to be remarked that autopsies show some of the fractures already united and some with callus present. This seems to indicate that actual fractures had taken place, and not that we had to do merely with numerous small separate centres of ossification which had not yet run together.

Symptoms. The symptoms consist, of course, in the occurrence of numerous fractures from insignificant causes. As a rule, the accidents are painful as in fractures in any other condition. In a few cases, however, it is stated that pain was slight. This was noticed, for instance, in the reports by Battles, Jones, Schultze, Dubrueil, and Blanchard (first and second cases). Pain preceding a break, such as may occur in osteomalacia, is entirely foreign to osteopsathyrosis. As to the bones most frequently affected, it is noticeable that the long bones of the extremities, as well as the clavicles and ribs, are those oftenest broken, and that fractures are especially frequent in the lower extremities. This last is doubtless due merely to the greater strain

put upon them. In no case is a fracture of a vertebra or of the pelvis distinctly mentioned, although possibly present in some of the cases of very numerous intrauterine fractures. The position of fracture is entirely independent of the relation of diaphysis and epiphysis. In very few instances was there even the supposition that the condition might consist in the separation of the epiphysis.

When refracture occurred it sometimes happened, as, for instance, in the patients of Willard and of Schultze, that the seat of old fractures was the position for new ones. But oftener the bones seemed to have broken irrespective of the position of former injury, and in the cases of at least two observers, Earle and Pauli, it is expressly stated that the seat of the old accident did not again fracture. In a few instances, as in the cases of Dupuytren and Langton, actual softening and yielding of the old callus previous to a new break seems to have taken place, but this was quite exceptional and anomalous, and must rather be called a complication than a symptom of the disease.

DIAGNOSIS. In making a diagnosis we have first to determine the absence of other conditions to which the fragility may be secondary. The exclusion of syphilis and of nervous diseases is of importance. Rachitis presents so many features apart from the breaking of bones that the diagnosis of this disease offers, as a rule, no difficulty. It is questionable whether true osteomalacia ever occurs at a very early age. It has, it is true, been described, as for instance, by Rehn (*Jahrbuch f. Kinderh.*, 1877, xii. 100), but Senator (Ziemssen's *Handbuch der spec. Path. u. Therap.*, 1875, xiii. I. 95) denies the existence of the disease in infancy; and it seems probable that Ziegler (*Lehrbuch d. path. Anat.*, 5 Aufl., ii. 123) is right in considering the reported cases to be really instances of rickets. At the least it can be said that osteomalacia would resemble rickets much more closely than it would osteopsathyrosis.

The absence of local lesions, such as osteitis, caries, tuberculous disease of bone, tumors of bone, etc., is also to be determined.

PROGNOSIS. The prognosis is, as a rule, very unfavorable. The duration of life does not seem to be materially affected by the disease, but the tendency to fracture, once established, is apt to continue unabated. In Mettauer's patient it seemed even to increase with years. The amount of crippling in bad cases may be very extreme. This was the condition, for instance, in Blanchard's first patient. We may,

however, always base a hope of improvement on the fact that a certain number of cases have distinctly outgrown the disposition to fracture. This was notably so in the cases of Axmann and of Graham, where the fragility disappeared by maturity. Some of the children reported by Willard also outgrew the tendency to fracture.

TREATMENT. In such a disease as this, in which both the cause and the nature are so little known, it is evident that the treatment can be but experimental. The administration of alteratives of various sorts, the maintenance of the best general health and the protection of the limbs against fractures are the indications most apparent, with the hope that as time passes the fragility may be outgrown. Still, while guarding against injury, we must at the same time see that the muscles do not waste. It is likely that a proper lack of muscular support to the limbs may itself increase the tendency to fracture. It is important in case of fracture to secure union of the fragments in proper position, in order to prevent malposition as far as possible. A number of cases have thus reached adult life with but little deformity; while others have grown badly misshapen for want of proper care.

DISCUSSION.

DR. H. M. LYMAN: I am reminded by this paper of a patient who was brought to my clinic some years ago, a young man about twenty-five years of age, who belonged to a healthy family, no other case of the kind having occurred among his relatives or ancestors. He was nursed by his mother during the whole period of lactation. He had no symptoms of rickets that I could discover. During early childhood he began to have fractures of the bones, and this condition of repeated fracturing of the long bones and clavicles had continued during childhood and boyhood. With advancing years the tendency to fracture had diminished. He had had thirty-three fractures in number, distributed over the long bones of the extremities and the clavicles. There was also some bending of the bones; the pelvis was somewhat distorted by bending, and the tibiæ were bent and rarefied. One of the tibiæ was translucent, so that if a lamp were placed on the distant side of the limb the light was visible through the bone very much as through a hydrocele. In his case there was probably an admixture of some of the phenomena of osteomalacia, differing from some of the cases related in the paper in that there was no hereditary disposition and no concurrence of the disease in other members of the family. There was great deformity consequent upon

these multiple fractures, and great retardation of growth. The patient seemed to be in perfect health; the head was well formed, his reason was perfect, and he spoke and talked of himself rationally. He was comfortable, had no pain, and slept well. His sexual organs were mature, but he claimed to be without sexual appetite.

DR. J. H. MUSSER: I would like to ask Dr. Griffith if he made an examination of the urine as to the quantity passed in the twenty-four hours. In a number of cases of rickets under my care the occurrence of polyuria was very marked, and in a case of carcinoma of the bone there was also polyuria. I am interested to know whether the symptom occurred in the affection in question.

DR. A. H. SMITH: With reference to the fragility occurring in advanced age I would like to mention that I once made an autopsy on a patient one hundred and eleven years of age. On opening the thorax the ribs were so soft that they were cut with ordinary scissors like soft pine. There had been no fractures.

DR. H. A. HARE: I happen to know something about the case of Dr. Griffith, nevertheless there are one or two points that are not clear in my mind. As I remember, in this case there is absolutely nothing in the history of the family which would show any trace of heredity. The maternal grandfather, whom I know very well, is a man of unusually fine proportions, very large, with well-formed bones. The mother is of unusually good bone-formation, and the father a stalwart, well-built young man.

The other point, which is not directly in connection with the paper, but which interested me, was this: I believe Dr. Griffith said that when the child was two days old it had an anæsthetic administered to it in order to discover a fracture. This is certainly a very youthful period for the administration of an anæsthetic. Did I understand this correctly?

DR. J. P. CROZER GRIFFITH: In regard to the anæsthetic I would say that the notes of the case were written out for me by Dr. Detweiler, and that they distinctly state that the child had the fracture on the second day of birth, that it was then anæsthetized, and that the other fracture was then found.

As to the family history, it is remarkably good—an exceptionally healthy family for several generations. There seems to be absolutely no reason for this child to have its peculiar trouble.

The condition of the bones of which Dr. Smith speaks is an interesting and extreme instance of what I suppose takes place frequently, to a less degree—the atrophy of advancing years. In the cases I have collected there was no atrophy whatever; in fact, there is usually nothing to account for the

fragility, chemically or microscopically. There seems to be something in the way in which the bone is put together which allows it to break.

As to the urine, there is only one of my cases in which an examination of the urine is reported. I was unable to get the urine of this child.

I may say in closing that there were in the Pennsylvania Hospital, a couple of years ago, two interesting cases of fragility in one family, with numerous fractures. I have not referred to them in my paper, because they have never been reported.

PAINFUL POINTS IN GOUTY, COMPARED WITH RHEUMATIC ARTHRITIS.

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THE differential diagnosis between acute gout and acute rheumatism is usually simple enough in typical cases, especially when of recent origin. In many chronic cases, however, particularly when gouty arthritis has become general, the differentiation may not be so easy, and in practice we frequently find gouty cases treated for rheumatism or rheumatic patients dosed with colchicum. For a number of years I have been accustomed to point out that a careful manipulation of the joints inflamed in these affections will show specific contrasts between them in the locality of the greatest tenderness on pressure. I supposed that this clinical fact had been noted before, but not finding any reference to it in the works which I have been able to consult, I take this occasion to present the following observations on cases of gout and of rheumatism occurring in my private practice, and in my service at the Roosevelt and Bellevue Hospitals of New York during the past few months.

GOUT.

Whole number of cases of gout, 34. Males, 27; females, 7.

The first attack, in the history of the patients, began in the lower extremities in 31, or 98.9 per cent. In two chronic cases the patients were uncertain where it first began. In one, a painter by trade, and affected with chronic plumbism, the first attack involved the left shoulder, as well as his feet.

The first attack was monoarticular in 73 per cent., and polyarticular in 27 per cent. I am inclined to think, however, that the percentage of monoarticular first attacks was higher, particularly in the hospital patients, for the memory of some of the more chronic cases on this point was rather indefinite.

The pulse was noticed as of high tension in 98 per cent., and not of high tension in 2 per cent.

The arteries were found thickened in 44 per cent., and not thickened in 56 per cent.

Tophi were present in the ears in twelve cases, or 35.1 per cent.

As to painful points, first, there were 38 instances of inflammation of the knees. In every one of these cases, without exception, the points of greatest tenderness on pressure were on the condyles. The more acute the inflammation the more distinctly is this tenderness pronounced. In the decline of the inflammation tenderness will persist there when it cannot be elicited elsewhere. This is in marked contrast with acute rheumatism, where, as we shall see, increased tenderness on the condyles, as compared with other parts of the joint, was not once found.

Of 23 cases of inflammation of the ankles, the points of greatest tenderness were found on the malleoli in 11, just below the malleoli in 10, and on the astragalus in 2.

On the great toe no uniformity in points of greatest tenderness was made out.

The hip-joint was affected in 2 cases, but without any localized tenderness to pressure in either.

In the upper extremity among the numerous phalangeal finger-joints affected, and in many instances distorted with gouty deposits, those of them which were painful enough to give indications showed, without exception, the points of greatest tenderness on the condyles; that is, on transverse pressure; while pressure between the dorsal and palmar surfaces did not occasion pain, or very slight pain compared with pressure on the condyles. I have found this in private practice a valuable sign, in women especially, as these joints are frequently in them the only ones involved in gouty inflammation.

The elbows were affected in 12 cases. Of these the most tender points were on the condyles in 6, on the olecranon in 4, and on both the condyles and the olecranon in 2.

The shoulders were involved in 5 patients, in 2 of them both shoulders were attacked. No particular point of tenderness was noted, except in 1, and that was on the acromion.

The cases of inflammation of the metacarpo-phalangeal joints were not enumerated, because their lateral tender points cannot be isolated.

The same applies to the wrists, but in both cases of these joints there is more tenderness to lateral pressure than in rheumatism.

Rheumatism.

Number of cases of acute rheumatism observed, 49. All of them hospital patients. Males, 32; females, 17

Among these the heart was or had been involved in 18, or 36.7 per cent. Tonsillitis occurred shortly before or during the attacks in 11, or 22.4 per cent. Pleurisy occurred in 3 cases, or 6 per cent.

The pulse is reported as of low tension or compressible in 42, or 85.7 per cent., of high tension in 5, or 1.02 per cent., and in 2 not stated. The first attack was polyarticular in 46, or 94 per cent.; monoarticular in 3, or 6 per cent.

In rheumatism, particularly when a joint is acutely inflamed, there is usually more superficial or cutaneous tenderness than in gout. This may mislead as to the existence of special points of tenderness unless the examination be made with particular reference to this subject, when in the great majority of instances, notably in some joints, rheumatism will be found to be scarcely less specific than gout in the localities of greatest pain on pressure, and what is equally important, that these are only in a few joints the same as in gout. Thus, in the knee the typical points of tenderness are on the tendon of the quadriceps, just above the patella, and below it also at the tendon insertion. Posteriorly, equally characteristic points of tenderness are found along the tendons of the hamstring muscles. Out of 58 cases of inflamed knees in my list, 53 were thus typical, or 91.4 per cent., and in 5, or 8.6 per cent. the pain was uniformly diffused over the joint. In no case were the condyles the seat of most tenderness.

Rheumatic inflammation of the ankles is not so distinctive in the location of painful points as in the case of the knees. Of 32 cases my notes are that the most pain was elicited by pressure on the tendons of the dorsal aspect of the joint in 20, or 64.4 per cent. This pain, however, is not as pronounced as in the tendons of the quadriceps and hamstring muscles of the knees. In 3 cases, or 10.6 per cent., the most painful points were under the malleoli, and in 8, or 25 per cent., there was no specialized place.

The hips were affected four times, but no localized pain was noted in either.

Of the joints of the upper extremity the shoulders were affected in 20 cases. Only in 1 of these was a special tender point found on the coracoid process.

The elbow was affected in 13 cases. Of these in 9, or 70 per cent., the most pain was elicited by pressure on the triceps tendon. In 4, or 30 per cent., there were no special points.

The wrists were affected in 34 cases. Of these the most pain was elicited by pressure on the tendons of the dorsal and palmar aspects in 20, or 83.3 per cent. It was uniformly diffused in 3, or 15 per cent., and in 1 case was most complained of on transverse pressure as in gout.

In every case noted of inflammation of the finger-joints in the rheumatic patients the pain was localized in the tendons, and not on the condyles.

Why the hips and shoulders do not commonly show specially painful points may be due to these joints being so covered by large muscles.

It seems natural to infer that the difference between these two forms of arthritis, in the respects noted of pain on pressure, is because gout chiefly affects the periosteal, while rheumatism chiefly attacks the synovial structures.

With the exception, therefore, of the hips and shoulders it would seem that the distribution of pain on pressure may often be of use in the differentiation of these two articular inflammations. The ankles and wrists also do not present such marked contrasts as the more simple joints, apparently from the greater number of bones entering into the formation of these articulations.

DISCUSSION.

DR. H. M. LYMAN: Sir Willoughby Wade, of Birmingham, England, sent me a little volume the other day on the subject of gout, in which he emphasizes very strongly this lateral tenderness upon the proximal side of gouty joints. He explains it by supposing that the nerves are inflamed as a part of the gouty process; and he is not so much inclined to implicate the periosteum as is Dr. Thomson.

DR. W. H. THOMSON: That must be a mistake with reference to the nerves, for on the condyles the nerves are not especially distributed, and that does not explain the difference between gout and rheumatism. I have had under observation three cases of gonorrhœal rheumatism, and in them there were no specific points of pain either upon bony prominences or upon the tendons, which is markedly different from the cases of others.

HABIT CHOREA.

By WHARTON SINKLER, M.D.,
OF PHILADELPHIA.

Gowers considers the term "habit chorea" a misnomer, and regards the affection as a form of spasm or tic, rather than a variety of chorea. The same view is taken by several other writers. Many authors, among whom are Strümpell, Hirt, and Gray, do not mention the disease at all. Weir Mitchell, who described habit chorea in 1881,[1] gave the following reasons why he regarded the affection as a form of chorea: first, the fact that it usually occurred in children; secondly, that in cases of habit chorea there are generally a history of some fall from the plane of health, and a state of irritability and nervousness; the circumstance that, in some instances, habit chorea lapses into well-pronounced chorea of the ordinary type; and, finally, that the same remedies which are most useful in Sydenham's chorea are of the greatest value in habit chorea. The largely attended clinical service at the Philadelphia Infirmary for Nervous Diseases has given me the opportunity of studying an unusual number of cases of habit chorea, and the result of this observation has confirmed my belief that Mitchell's view as to the nature of the affection is correct. There are undoubtedly cases to which the term habit spasm is properly applied, and I believe these cases are properly classed with the different forms of tic. I think that the differences of opinion as to the disease are mainly due to the fact that there are two varieties of habit chorea. The first is one in which the disease is evidently the result of a trick or habit in a child or adult, while in the second class the affection is due to some predisposing cause, such as is operative in the production of Sydenham's chorea.

The movements in both forms are much alike in character and

[1] Lectures on Diseases of the Nervous System, Lecture VIII.

extent. In both the irregular movements and spasmodic twitchings are like those of chorea minor, but are confined to a limited region of the body. They cease during sleep, are increased by excitement, and may or may not be controlled by an effort of the will. The movements in habit chorea are unlike the spasmodic twitchings which occur in the different varieties of tic, and this difference may be notably seen by comparing a case of facial tic (tic convulsif) with a case of habit chorea which affects the upper facial muscles. In habit chorea the onset may be abrupt or gradual, and the irregular movements are confined to one portion of the body. In the majority of cases the region selected is the face. The spasmodic twitchings occur at intervals sometimes of a few minutes, or the intervals may be so short that the movements are almost incessant. There may be blinking of the eyes, or a sudden contraction of the orbicularis palpebrarum, or depression and elevation of the eyebrows may occur. A common symptom is contraction of the zygomatic muscles, moving the angles of the mouth first to one side and then to the other. Movements of the head often occur, such as rotation and nodding, or jerking the head backward. In other cases there is shoulder shrugging. More rarely leg movements occur, such as the sudden extension of the leg and irregular contraction in the thigh muscles, which may occur in walking, giving rise to a gait like that of a "string-halt" horse. In other cases the respiratory muscles are involved, and various disordered sounds are emitted by the patient. Sometimes these sounds are merely slight grunts, in other cases there is an irregular hacking-cough, and occasionally an explosive utterance is made, which may be loud and annoying. Gowers relates a case which began with irregular laryngeal sound, lasting two years, at the end of which time the whole left-half of the body became affected with choreic movements, and these lasted for a year, when complete recovery took place.

Some of the forms of habit chorea, especially those which arise from a trick, are very odd. One patient at the infirmary, a girl, aged sixteen years, who had had a previous attack of chorea minor, acquired the habit of rubbing the toe of her shoe against the calf of the other leg. This would occur while walking. She would stop for an instant and rub the toe against the calf of the other leg, and then go on as if nothing had happened. Another case, which Dr. T. G.

Morton kindly sent to me, had had a habit for about three years of rubbing the eyebrows. She began at first to rub the brows on account of slight itching, and soon acquired the habit of rubbing the brows whenever not occupied with her work or otherwise. If she was reading the brow-rubbing was almost continuous, and, as a result, the eyebrows on both sides had been as completely removed as if they had been shaven. A curious form of this affection came on in a little boy of five, who began by imitating the movements made by the motorman of a trolley car, and it soon became a habit which required some efforts on the part of the parents to break. He would stand with his back to a door, first swinging around one arm, then the other, and would make an explosive utterance. A very singular case was that of a boy of twelve years, two of whose aunts had suffered from a form of habit chorea. The boy began two or three months before he was seen to make choreic movements of the toes. He would twist the toes over each other, and untwist them continuously. The toe movements continued for several weeks, when they ceased, and similar movements began in the fingers. He kept up the finger movements for a couple of months, when they ceased, and he began to make movements of the mouth and neck muscles. When the patient was seen the mouth was opened and shut at intervals, and the platysma on either side was thrown into irregular contractions, drawing the chin downward and upward. The head would be occasionally thrown backward, and there was a condition of general unrest. In some cases the habit seems to acquire the form of an imperative mandate, the patient resisting the impulse to perform the act for some time, and finally being obliged to yield to it.

Often habit chorea arises from nasal disorder, which gives rise to sniffling or distortion of the facial muscles. In the greatest number of cases, however, some ocular defect, either as a refraction error or disease of the lids, is responsible for unnatural blinking, orbicularis contractions, or movements of the upper facial muscles. It is not infrequently the case that muscles over which there is not usually voluntary control, such as the occipital frontalis and ear muscles, are affected with involuntary movements which seem to have originated in voluntary movements by the patient. I have seen two or three cases in which contraction of the occipito-frontalis caused active twitching of the scalp, and I know a case in which the ears are

moved in sympathy with nasal sniffling and contraction of the facial muscles. One evening at the theatre I sat behind a lady whom I knew to have chorea of the occipito-frontalis. She wore a bonnet in which there was an ostrich feather, and with every movement of the scalp there was an extensive waving of plumes. Two patients of mine acquired a choreic movement of the shoulders as a result of first wearing suspenders. A sensation as if the suspenders were falling off, caused shrugging of the shoulders, and this movement persisted for years. In several other instances a tight collar was responsible for the beginning of the habit. In the other class of cases, in which no trick or habit is responsible for the affection, the movements are simply those of chorea minor, but are limited to the face, the shoulders, or, perhaps, the leg.

With the assistance of Dr. Frank Savary Pearce I have made an analysis of all the cases of chorea which have been treated at the Philadelphia Infirmary for Nervous Diseases from June 9, 1876, to April 15, 1896. During this period 1059 cases of chorea have been treated at the clinics, of which 143 were recorded as cases of habit chorea, and the vast majority of the remainder were chorea minor. Previous to the description of habit chorea by Dr. Weir Mitchell, in 1881, all cases of chorea coming to the infirmary were recorded under one class, but a careful *résumé* of all cases, and the subsequent histories which have been obtained, have enabled us to include almost every one in which a habit chorea existed alone or which occurred as a sequela of true chorea minor.

In dispensary practice it is impossible to obtain satisfactory data as to result of treatment. As soon as the patient recovers, or, in fact, when marked improvement has taken place, he usually ceases to attend, and it is only when a patient returns with a second attack of the affection that anything is known of the result of previous treatment. We have sent a large number of postal cards to cases of chorea, asking them to return to the hospital for further examination, but only about a dozen cases have reported. A large number of postals were returned, so it is presumable that the majority of patients have changed their addresses. It is fair to assume, however, that many of these patients have recovered or have outgrown the conditions for which they came for treatment.

Age at onset of the affection. In 2 of the 143 cases of habit

chorea the age was not noted. The ages of the remaining 141 cases are given in tabular form:

Age.	No. of cases.	Per cent.	Age.	No. of cases.	Per cent.
1 year.	2	about 1.50	13 years.	14	about 10.50
2 years.	2	" 1.50	14 "	5	" 3.50
3 "	4	" 3	15 "	1	
4 "	4	" 3	16 "	4	
5 "	10	" 7	17 "	2	
6 "	8	" 5.50	18 "	1	
7 "	10	" 7	21 "	1	
8 "	16	" 11.50	25 "	1	
9 "	15	" 11	37 "	1	
10 "	12	" 5.50		—	
11 "	17	" 12	Total,	141	
12 "	11	" 8			

Studied by hemi-decades the onset of the affection was found to have occurred

During the first hemi-decade in	22 cases.
" " second hemi-decade in	61 "
" " third " "	48 "
" " fourth " "	7 "
" " fifth " "	3 "

No case in our series began after the age of thirty-seven years. It will be seen, then, that of the 141 cases, 109, or about 77 per cent., began during the ages of five and fifteen years.

Duration of the disease before the patient reported for treatment. This ranges from a few weeks to from three to five years. In a few cases the disease had lasted for as much as nine years before the patient was seen.

Relation to sex. The affection seems to have but little predilection to sex. Of the 143 cases, 74 were males, and 69 were females.

Heart lesions. In 32 cases cardiac murmurs were noted. It is probable that a careful examination was not made for heart disease in the examination of all cases, for the absence of cardiac disturbance was not always noted. In the cases in which heart trouble was recorded, in 19 soft systolic murmurs were heard over the the mitral area, and feebly transmitted, if at all. In 1 case a loud systolic murmur was noted. This case had also a pulmonary murmur. In

3 cases pulmonary systolic murmurs were heard. In 6 cases aortic systolic murmurs were heard, and in 2 aortic regurgitant murmurs were present. In 1 case there was probable mitral stenosis. Anæmia is not as frequently present in habit chorea as it is in Sydenham's chorea, and, therefore, fewer hæmic murmurs are heard.

Influence of volition. In most cases voluntary effort controls the movements temporarily, and the patients usually show less movement during the attention required of them during the recording of their histories than do cases of chorea minor.

Seasonal relations. The season of year seems to exert little or no influence upon the production of habit chorea. In 106 cases the incipiency of the disease was noted. In these 34, or 32 per cent., began in winter; 23, or 22 per cent., began in spring; 28, or 26 per cent. began in summer; 21, or 20 per cent., began in autumn.

Occasionally one meets with cases in which there is a tendency to recurrent attacks in the spring. Dr. G. E. de Schweinitz had a patient in whom an attack of habit chorea returned every March, until its recurrence was anticipated by the administration of arsenic, and thus prevented.

Supposed causes as given by patients or friends. In only 63, or 44 per cent., of the cases was a cause assigned or determined. The causes given are as follows:

Anal fissure	1	Injury	2
Bathing excessively	1	Irregular menstruation	1
Collars too tight	2	Over-eating	1
Cholera infantum	1	Physical overwork	2
Coffee in excess	2	Overwork at school	13
Domestic trouble	1	Smoking	1
Fright	12	Surgical operation	1
Grippe	2	Swimming	2
Habit or trick	4	Suspenders	1
Imitation	6	Teeth decayed and cutting	3
Infectious diseases	5		

In one case, which was alleged to be due to fright, the patient had had an attack of chorea minor six months previously. In two cases in which the disease seemed to have originated from dental irritation, in one the patient was cured after the filling of the teeth, and in another after the eruption of the teeth. In the case of a woman who

had for many years habit chorea, the affection ceased during pregnancy, to reappear after childbirth.

Parts most commonly affected. The eyelids are most frequently involved, then the facial muscles, and next the head and neck. Sudden, general twitching or jumping of the electric type is the most rare form. Below is given in tabular form the number of times different parts were affected in the cases recorded:

Eyes alone and combined	72,	about 18	per cent.
Mouth or tongue	37,	" 9	" "
Face and nose (as grimace, snuffing, etc.)	54,	" 13	" "
Scalp	6,	" 1	" "
Neck and head	56,	" 14	" "
Stammering or disordered speech	16,	" 4	" "
Shoulders	35,	" 8	" "
Hands	26,	" 6	" "
Arms	36,	" 9	" "
Feet	15,	" 4	" "
Legs	25,	" 6	" "
Jumps or stops suddenly (electric)	2,	" 0.184	" "
"Grunts"	3,	" 0.368	" "
Rotation trunk	4,	" 1	" "
General	2,	" 0.184	" "
Total of number parts actively involved	389	100	" "

Optical defects. In many of the earlier cases no examination of the eyes was made for refraction errors, but of the recent cases 49 were carefully examined by Dr. G. E. de Schweinitz and Dr. A. G. Thomson, to whom I am indebted for the careful study of the ocular defects in these cases. The report of these gentlemen gives the following disturbances of the eyes: 15 cases of hypermetropia, with astigmatism, 2 of which were complicated by conjunctivitis, due to eye-strain; 2 cases of myopic astigmatism; 2 cases of uncomplicated astigmatism; 20 cases of simple hypermetropia; 2 cases of simple myopia; 2 cases of conjunctivitis; 6 cases of defects in ocular balance. Of the 49 cases 8 were apparently cured by glasses. Many did not accept the advice to have glasses fitted, and many did not report the result of treatment.

Effect of school in causing habit chorea. Of the 143 cases of habit chorea, in 35 it is recorded that the patients were attending

school. It, therefore, seems that like chorea minor many cases of habit chorea are school-made.

Relation of habit chorea to Sydenham's chorea. In 9 cases attacks of chorea minor had preceded the habit chorea, and in 2 cases habit chorea coexisted with an attack of Sydenham's chorea.

Nasal irritations. Obstructive diseases of the nose were found to be common complications, and are to be regarded as causes by favoring facial movements. Two or three cases were cured by nasal treatment. In one case hypertrophy of the turbinated bones, and in another case enlargement of the tonsils were noted as probable causes. In one case epilepsy co-existed, and in two cases night-terrors occurred. In many cases there was anæmia, but this condition was not as common as it is in chorea minor.

Prognosis. The prognosis in this affection depends largely upon the length of time it has lasted before the patient is seen. In a great proportion of cases, if seen early enough, the disease may be completely and permanently cured. In adults in whom the disorder has lasted for some time it is difficult, if not impossible, to arrest the movements. All of us are familiar with instances among our acquaintances which we have observed for many years, and which appear to be a fixed and permanent part of the individual. Habit chorea has a tendency not only to become uncontrollable the longer it lasts, but also to increase its range and involve other groups of muscles.

Pathology. There is no proof that any lesion exists in the brain or spinal cord in these cases. It is probable that the groups of nerve-cells which supply the affected muscles acquire a habit of discharging at irregular intervals independently of any control of the will.

Treatment. The majority of cases depend upon some distinct and positive cause, which careful investigation will usually discover. It is essential, therefore, in every case to determine the existence of a cause, and to take measures for its removal. In cases of long-standing, however, it is not sufficient merely to get rid of the cause, for the nerve-centres having acquired a vicious habit do not recover their normal condition until systematic treatment has been pursued. This is especially observable in those cases in which habit chorea has resulted from an error of refraction. The experience of de Schweinitz and Thomson has entirely coincided with my own in this respect. It has been found that medicinal treatment alone seldom arrests the choreic

movements. On the other hand, merely correction of the refraction does not cure them. It is necessary, therefore, first to correct the ocular defect, either by glasses or tenotomy, and then to pursue a course of medicinal treatment. The same statement applies to those cases in which nasal or throat disease has been the cause of the affection.

In nearly all cases the general health is at fault. The patient is anæmic, or he is run down from over-study, improper food, or some attack of illness. The point of first importance, then, is to look carefully after the general health. Tonics, more especially chalybeates, should be administered, and, if possible, change of air is to be obtained. In school children it is usually necessary to stop study for a time.

The one drug which seems to exert a special influence upon the disease is arsenic, and it should be administered in the same manner as in the treatment of chorea minor. It is seldom of value when given in small doses, but it should be administered in gradually-ascending doses until some toxic influence is observed.

Many years ago Weir Mitchell called attention to the fact that some cases of habit chorea which were not relieved by the internal administration of arsenic were cured by its exhibition hypodermically, and this method of treatment continues to be successfully used at the Infirmary for Nervous Diseases.

The question as to whether the patient should be urged to control the movements by an effort of the will, and also as to whether in the case of children any form of punishment should be used, are mooted points. My own belief is that in all cases the patient should be induced to bear in mind continually the occurrence of the irregular movements, and to make every effort to check and control them. Any form of punishment for the movements in children is to be deprecated, but in every case much can be done by the promise of reward. In almost every child who is suffering from habit chorea much benefit will be derived from offering a premium whenever the movements are controlled for a certain length of time.

In all cases it is important to secure as quiet and uneventful a life as possible, and removing the patient from work or exciting sports is necessary in many cases. The most speedily beneficial results are obtained by a modified course of rest treatment. I have frequently

seen cases which have resisted the ordinary course of medicinal treatment at the clinics make rapid improvement when admitted to the hospital and placed in bed.

DISCUSSION.

DR. OSLER: I do not like to let this paper pass without lifting my voice at least against the expression of opinion which is contained therein. I think this is a step distinctly in the wrong direction. We have of late years learned to separate the habit spasms or tics from true chorea. Personally I think they are entirely different. I willingly admit that there are many cases in which it is very difficult, almost impossible, to say whether the condition is one of chorea minor or of habit spasms, but in the great proportion of cases the two affections can be separated from each other. In habit spasms the character of the movement is very often entirely quite different. The symptoms persist for a very much longer period of time, and rarely, if ever, in my experience, is endocarditis met with; this, I believe, to be a most important point. Moreover, who has seen in connection with a simple Sydenham's chorea the curious psychical phenomena so commonly observed in cases of habit spasm, the echolalia and coprolalia and other forms of obsession, which are so extremely common? This entire class of cases can be separated from Sydenham's chorea. The work done by the French school on this question is first-class, and should be followed very closely by the students of neurology.

DR. J. J. PUTNAM: I can only second what Dr. Osler has to say. I think that habit chorea certainly belongs to the degenerative diseases of the nervous system far more than ordinary chorea does, although, in spite of the fact that the ordinary chorea sometimes originates in fright and may possibly have some toxic origin, it nevertheless does depend upon a peculiar predisposition of the nervous system.

Dr. Morton Prince, of Boston, has described on several occasions a form of trouble which should be mentioned in this connection—what he calls an "association neurosis." He tries to explain in a philosophic way the persistence of symptoms which were originally due to some special cause. The origin of some cases of habit chorea certainly makes one feel justified in ranging that in the same general category.

DR. S. WEIR MITCHELL: I am the putative parent of this form of disease. I never held very strongly to names in my life, and think the name of this affection does not matter materially. I have been glad to have had the pleasure of discriminating this clinical group as apart from others. I certainly have seen cases of chorea pass into habit spasm or leave children with habit

spasms. I have many times in my life seen the habit spasm begin as such and pass more distinctly into a condition of chorea minor. Dr. Sinkler's paper, instead of showing that there was no kind of relation between abnormal conditions of the heart and habit spasm, seems to show, to my surprise, that there is a considerable amount of it; if I did not misunderstand his paper there was about 35 per cent. What amount of these had other diseases to account for the heart condition it might have been well to state in order to elucidate matters.

DR. H. A. HARE: I hesitate to speak on this subject in the presence of those having vastly larger experience, but I have had a case recently which I believe is of interest in this connection. A boy under my care at the present time was struck with a base-ball bat on the forehead when he was seven years of age, which was ten years ago. Ever since that time he has developed a very curious movement which is not associated with echolalia or coprolalia. It is a sort of spasm of the muscles of the mouth which causes him to make a hissing sound with almost every movement of the body. The movements are quite distinct from those we see in ordinary chorea minor, reminding you of the cases described as Dubini's "electric chorea" or Bergeron's "electric chorea." The contractions are like those following muscular stimulation by electricity. It seems to me that these cases of chorea minor (if there is any truth at all in the belief that a certain number of them are dependent upon some infectious cause) are separated from the cases of habit chorea which apparently are imitative and not infectious, and for this reason it is hardly possible that the two classes of cases can be grouped together.

DR. JACOBI: The principal symptoms enumerated by Dr. Sinkler belong to the face and forehead, the blinking, and winking, and the twitching of the angles of the eye, and the muscles of the nose and mouth, the frowning, the shrugging of the shoulders. I have seen a good deal of that, and described it in the *American Journal* in 1886. I called it at that time partial and sometimes general chorea, produced as symptoms of nasal reflex. I again wrote on the subject in the *Festschrift* for the celebration of the seventieth birthday of Henoch, 1890. My observation is simply this: The majority of cases of partial chorea and habit spasm, principally occurring upon the face, are the result of chronic and nasal and pharyngeal catarrh. These reflexes are all within the territory of the trigeminus and the facial. It is but seldom that they go beyond the face and head. Sometimes they will extend to the shoulders, and, in very rare instances, all over the body. Sometimes, but rarely, they remain unilateral. Most of these cases are seen in children below ten years of age. I can now say that nine out of ten cases get nearly well simply through local treatment of the nose and naso-pharynx. It is true that a large number of cases require arsenic, for, when the habit is once established and has lasted a year or more, arsenic in increasing doses is required. As a rule, by properly cleansing the nose with salt water and an occasional application of a solution of 1 to 10 per cent. of

nitrate of silver the symptoms will be relieved. In rare cases only surgical work is required, for it is my experience that congenital deviation of the septum is a cause of this "habit spasm" less frequently than catarrh, erosions, and hypertrophied soft tissue.

DR. SINKLER: I have nothing to add, except to say that in my paper I called attention to the fact that there were two varieties of habit chorea, one which was a partial Sydenham's chorea confined to one region of the body, which might extend into a general chorea, and the other, which was a habit or trick, resembling the tics. I do not think that the trick form is like a spasm, and the accidental association of coprolalia or echolalia with it certainly does not change its character, for we see this disorder of speech in other forms of chorea.

ON PERIODICAL NEURALGIAS OF THE TRIGEMINAL NERVE AND THEIR RELATION TO MIGRAINE, WITH SPECIAL RELATION TO THE INTERMITTENT SUPRAORBITAL NEURALGIA.

By JAMES J. PUTNAM, M.D.,
of Boston.

Whenever investigations are being made for purposes of classification, whether in the department of natural history or in that of medicine, two tendencies are always obvious, one of which leads the investigator to recognize the resemblances between the various objects of his examination, while the other leads him to see the differences between them. These tendencies are never more noticeable than when the diseases of the nervous system are at stake, and they have frequently made themselves felt as regards the study of migraine in its relation to other painful affections, especially those which are ordinarily designated as neuralgias.

Anstie, a master of intelligent analysis, and whose writings are still sound, fresh, and vigorous, defined migraine as a form of trigeminal neuralgia, having, of course, in mind simply the pain element in migraine of the common form. Thomas,[1] a clear-headed and intelligent observer, and various other writers, take the same view, while equally good authorities[2] hold that there is no excuse for confounding migraine and neuralgia with each other.

The truth is that we lack a satisfactory touchstone for each of these affections. We are ignorant of their pathology, and have no really good theory of their meaning as phenomena of nervous activity. That they present points of clinical likeness to each other is obvious, and we are likely to gain as much from tracing these out as by accentuating the

[1] La Migraine, Paris, 1887, pp. 94 and 97.

[2] Compare Moebius; Nothnagel's Specielle Pathologie. Migräne, p. 70.

points of difference between them. In my own belief, both of these painful disorders are to be interpreted as caricatures, so to speak, of physiological or quasi-physiological events. They are probably exaggerated bits of the emotional complex. The pain is only one element in both affections.

While some of the cases of supraorbital neuralgia would be declared by many physicians to stand in no real relationship to migraine, there are other cases of very similar type, which, without greater reason, as I think, would often be simply classified as special forms of migraine.

The literature of migraine has become too unwieldy to be referred to here in detail in relation to this question, but, fortunately, it has been enriched within the past year by a summing up at the hands of Moebius, of Leipsic, which is remarkable for its clear, comprehensive, and unequivocal statements.

The symptoms of this great disease are so numerous, and their grouping is so various, that one is under the temptation to save himself the trouble of setting off special symptom groups, if only they have something of the migrained character, by simply classifying them as varieties of migraine, just as the suburbs of a great city easily get to be called by the name of their centre. If one looks at the matter more nearly, however, and especially if one happens to be particularly interested in clinical study of a special symptom, it becomes evident that a good deal of reclassification is often both possible and profitable, and that, after all, the symptoms which go to make up migraine are not, like the parts of a machine, without an identity of their own, but are to be compared rather to the individuals who compose a shifting crowd, yet remain liable to enter into new relations.

Looking at the matter from this point of view, I wish to call your attention to the migrainoid characteristics of certain forms of the trigeminal neuralgias, especially the intermittent supraorbital or ophthalmic neuralgia, and, at the same time, to the fact that, after all, these affections are not identical with migraine.

The intermittent supraorbital neuralgia is an exceedingly interesting affection, and one which has been described by various writers, and under different names, but it does not receive in text-book literature the attention that it deserves. One reason for this is that which I have already indicated, namely, that some of the cases have been

merged in migraine, and we may infer that Moebius would justify this view, both from the general trend of his remarks and from his reference to importance of frontal sinus and nasal catarrh as an occasional cause of migraine. Other cases, again, have been merged in malaria, which some of the older writers considered as the essential cause of the outbreaks. As a matter of fact, however, the malarial influence, in this country at least, is of but little account.

The intermittent or migrainoid form of supraorbital neuralgia is to be sharply distinguished from other forms of neuralgia having the same seat, and if we could determine the reasons for this difference we should be making a long step toward a better understanding of migraine. Thus, one sometimes sees a typical neuralgic tic of the supraorbital area, like that so common for the lower branches of the fifth, and forms of supraorbital neuritis associated with serious trophic disorders, which are highly interesting and place in a stronger light the importance of the functions of the fifth nerve. Of these affections I cannot now speak in detail. It is, however, noteworthy that analogous differences exist between the types under which the painful affections of other areas of the body occur. To a great extent these differences are determined by the presence or absence of peripheral causes of irritation on the one hand, and of central tendencies on the other hand. And "central tendencies" mean structural peculiarities of the central nervous system, generally of hereditary or developmental origin, and having a physiological meaning. The more strongly marked is the tendency to periodical recurrence of any sort of nervous outbreak, even though the outbreak would not occur at all without some slight peripheral cause, the greater is the reason to suspect that central influences are at work, and to look for other signs of nervous instability.

It is probable that all the periodical neuralgias, and also the visceralgias, are, like true migraine, to which they are often so nearly related, signs of what, for the purposes of scientific classification, may be called a degeneracy of the nervous system.

The literature of the intermittent supraorbital neuralgia is not very extensive, but contains some important contributions. A Paris graduation thesis by Dr. Ernest Faucheron,[1] published in 1880, gives a

[1] De la nevralgie sus-orbitaire considérée dans ses rapports avec l'œil, Paris, 1880.

reference to a Latin dissertation on the subject by a Daniel Ludwig, written as early as 1672, and others by Van Swieten and by Morton, about the middle of the seventeenth century. The earliest reference given in the *Index Catalogue* of the Army Medical Library is to a paper by a French writer—Rennes,[1] of Bergerau—who describes a sort of epidemic of this malady, due, as he thinks, to malaria. He had seen thirty-two cases in a little over one year, and all in private practice. A careful analysis would probably show that this collection could profitably be subdivided; but Bertherand,[2] a French army surgeon, also saw, in 1847, a group of eleven cases within one month, at a village in Northern Africa.

Dr. James Jackson, in his *Letters to a Young Physician*, published in 1855, gives an account of this interesting form of neuralgia, which, though short, bears the stamp of clearness which characterizes all his work. He calls the disease intermittent hemicrania; and though he distinguishes it from migraine, he points out that the pain may involve not only the supraorbital area but also the temple, and even, though exceptionally, the back of the head. Dr. Jackson was one of the first to note that these attacks are usually provoked by nasal catarrh, and are often curable by quinine or arsenic in large doses.

Another graduation thesis, this time from the University of Giessen, by Theodor Welcker, published in 1869, gives an excellent account of the whole subject, and an analysis of twenty-five cases, most of which are cited from other writers. He, also, rejects malaria as the principal cause, and invokes instead acute catarrh of the air-passages, but without analyzing this factor at any length.

Mendach,[3] an ophthalmologist of Zurich, writing in 1879, reports that eighty-two cases had been treated in twenty years at the Canton Hospital, though the region was free from malaria. He was the first, I think, to study with care the interesting seasonal relationships of the affection, and gives a plotted curve which indicates that the frequency of outbreaks begins to increase rapidly in the latter part of autumn, reaches its culmination in February, and then declines. The winter season is, he says, the period of maximal catarrhal tendency likewise, and therein lies the explanation. This question will be referred to again later.

[1] Arch. gen. de méd., 1836, 156.
[2] Cited by Faucheron.
[3] Correspondenzblatt für Schweize Aerzte, 1876, ix. 640.

Of the later writers, I would refer especially to Eulenburg,[1] Anstie,[2] Seeligmüller,[3] Gowers,[4] but without attempting to make the list exhaustive. The impulse given to the study of neuroses of naso-pharyngeal origin, especially by Hack,[5] about fifteen years ago, also had important results, though it is probable that Hack went much too far in ascribing such importance, as a cause of reflex symptoms, to simple swelling of the nasal mucous membrane. At any rate, Hartmann,[6] of Berlin, probably came nearer the true etiology of this particular form of neuralgia in referring it to irritation in the frontal sinus, which he thinks is due to diminished air-pressure arising from occlusion of the nasal duct by secretion or swelling and subsequent air-absorption, such as occurs in the case of the middle ear. This cause and the possibility, which Hartmann claims to exist, of giving relief by inflation are at least worth bearing in mind. Hack reports an interesting case which reinforces the view that even where the local cause is predominant, hereditary tendencies are often found lurking in the background. The patient was of strongly neuropathic temperament, and had at times vibrating [migrainoid] scotomata. The pain also had a slight tendency to shift sides. Yet if, in these respects, the case approached the migraine type, in others it was distinctly neuralgic, and the pain was markedly increased both by pressure on the nerve-trunk and by superficial contacts with the skin.

As regards the frequency of these cases in this neighborhood, the records of the Massachusetts General Hospital show an aggregate of about a dozen cases during the past year, the majority of the patients having presented themselves during the spring months.

A comparison of my experience with that of the authors cited, and others not referred to, justifies the following clinical sketch of the disease:

The attack is apt to be ushered in by a dull feeling in the whole forehead; or by some form of paræsthesia in the frontal area of the affected side; or by a localized sense of heavy pressure at the nerve-exit under the eyebrow; or by an enlargement of the pupil, letting in more light than usual to the affected eye; or by a feeling of dryness in one nostril.

[1] Nervenkrankheiten.
[2] Neuralgia and its Counterfeits.
[3] Krankheiten der Peripheren Nerven.
[4] Diseases of the Nervous System.
[5] Wiener med. Wochenschr., 1882, 51.
[6] Berl. klin. Wochenschr., 1882, 732.

Even the day or perhaps several days before the outbreak some warning may be felt, such as a general sense of depression, with dull head. In one case, to be referred to later, the face of the opposite side, and both limbs feel prickly or numb or heavy; but this case ought perhaps to be classed as migraine. Frequently, the patient feels well throughout the attack except for the pain. When the attack is at its height the pain is liable to be distributed over the whole frontal nerve-area, the eye, and the side of the nose, and the kinship of the affection of migraine is shown by the fact that painful areas may be found in the temple, near the vertex, and even at the back of the head.

Occasionally the lower branches of the fifth or the forehead of the opposite side are involved.

The eye becomes reddened and weeps; the pupil is generally dilated, but is sometimes contracted; the lid droops; the muscles of accommodation and even the external muscles of the eye may become paretic; and signs of flushing occur.

In light attacks the pain may be definitely localized in one spot—the eyeball, the eyebrow, the forehead. In character the pain is boring, deep-seated, or painfully pulsating. Tinnitus aurium, sweating of the skin, and other nervous symptoms may complicate the attacks. If the pain is severe vomiting comes on.

In the thesis of Welcker a case is recorded where the vision on the affected side was greatly obscured, and "glimmer" scotomata seem to have been present in a few cases. Here, again, we touch on the realm of migraine; but all that I claim is that sharp division lines could only be arbitrarily drawn.

As a final outcome of repeated attacks, the eye may remain permanently more liable to fatigue, the arterioles of the affected frontal area may perhaps become more or less thickened [Thoma], and signs of impaired nutrition of the skin and periosteum may appear. Here we touch hands with the cases where neuritis is the chief lesion. I know of three typical cases where slight thickening occurred over the eyebrow, apparently involving the periosteum, and in one of these, long after any attack had been present, small but tender papules used to crop out, scattered in small numbers in the eyebrow or on the forehead.

The pain is, as a rule, regularly intermittent, the recurrences taking place usually in the morning at eight or nine o'clock, less often

in the afternoon, and only occasionally in the evening. Sometimes, and that especially in seizures of long duration, there are two recurrences in one day, the second being always the lighter; and, as in the case of migraine, the type of recurrence may change in the course of years. Very rarely, instead of a distinct intermittence, only a remittance of the symptoms occurs. The attacks occur in groups, spread over one to several weeks, or even very much longer periods, provided the local [catarrhal] irritation persists, or the nutrition of the nerve is impaired, or the neuralgic habit is formed. The outbreaks generally recur daily. It is said that in some cases there are regular intervals of two or three days, but this I have never seen. The frequency with which the groups of daily attacks recur is partly, but not wholly, dependent upon the frequency of recurrence of special causes. The observations of Mendach have already been quoted, according to which by far the greater number of attacks occur, at Zurich, in the winter, and this pretty nearly reflects my own experience, though I have known them to occur in the late spring and in the fine weather of summer. Another writer has observed cases showing regular recurrences every spring and autumn for a series of years. One patient, a physician, whom I have examined, but of whose case I have, unfortunately, no notes, had had regular attacks of this sort for some twenty years, and had been driven by them to desperation. Another patient, otherwise a strong, healthy man, had had an attack every year for four years, and always in March, except last year, when it occurred in August. It is doubtless true, as Mendach says, that this tendency is partly controlled by the fact that catarrhs are more common in winter, but it is also certain that the habit of cyclical recurrence makes the nervous system more susceptible at certain periods. It is generally possible to trace the actual outbreak to catarrh of the frontal sinus, but, sometimes, even with persons whose attacks are usually brought on in this way, an outbreak occurs for which special causes are sought in vain. It is even conceivable that the cold and damp weather, when it does cause coryza, effects this result by acting first on the predisposed segment of the nervous system, and through that on the nasal mucous membrane, the vitality of which has been lowered. It is certain that it is not every attack of catarrh that ends in neuralgia, even with a predisposed person. As has been said, it seems to be the catarrh of the sinus which is specially

related to these seizures, and consequently they usually occur, as might be expected, rather late in the course of an ordinary cold in the head, unless where, as in a violent epidemic influenza, the whole nasal tract lights up at once in inflammation. Sometimes the catarrh, involving the frontal, sphenoidal or ethmoid sinus, or the antrum, becomes chronic, and in such cases the neuralgia also may persist in full violence. I watched for some time a case of this sort that Dr. R. H. Fitz was kind enough to refer to me.

The patient was a man of good general health, a farmer, married, and thirty-nine years old. Toward the end of September, 1894, he had a catarrhal attack, attended with great prostration. After this had continued for about a week he began to suffer from diffuse frontal pain such as frequently accompanies the extension of inflammation into the frontal sinus, but in an unusually severe form. For two weeks he remained in the house, suffering night and day. As he grew better the pain changed its character and seat. At first it diminished in intensity toward nightfall and began to be limited to the left side of the forehead; then it ceased altogether for the night; and very soon the attacks began to assume the type which they continued to show for a number of months afterward—that is, with a recurrence of pain at eight or nine each morning, and a duration of six to eight hours.

This case is interesting from several other points of view. In the first place, the patient himself used to have "sick headaches" frequently when younger, and still continues to have them to some extent, usually about once a month. His mother was also a sufferer from migraine. I shall adduce other cases, later, to show that a tendency of this sort is almost always to be found in the personal or family history of patients with this intermittent form of neuralgia. It is also interesting to note that the purulent secretion was very profuse on the affected side during the attacks of the pain, and began to grow less when the pain abated, disappearing almost wholly toward night. I have recently seen another case where, by the account of the patient, the secretion was never noticeable except during the attacks of the pain, so much so that he at first denied that he had any catarrh at all. His final statement that he had an occasional discharge of thick muco-pus during the attacks, and on the affected side alone, was verified by an examination made at the hospital. I do not think, however, that the pain necessarily disappears when the local inflammation ceases, and Dr. Algernon Coolidge, who kindly examined and treated for me the patient whose case I have related above, is of the same opinion.

Hartmann[1] has reported an interesting case with severe catarrhal symptoms closely like those which I have just described.

Cases of supraorbital neuralgia of malarial origin, the true "brow ague," are very rare among us. I have notes of but two where that seemed a possible cause. It is also not unlikely that the importance of this factor has been overrated abroad. Delame[2] reports a case where the malaria preceded the neuralgia by five years, which, perhaps, amounts to saying that there was little connection between the two.

Finally, the question comes up as to the relation of this form of neuralgia to migraine, and as to its dependence upon an hereditary tendency.

The cases that I have seen range themselves, in this respect, in the following groups: 1, those in which no migrainoid or other special neuropathic tendency is traceable; 2, those where other members of the family have had this same form of migrainoid neuralgia with perhaps a touch of true migraine; 3, those where the patient's attacks and those seen in other members of the family approach very nearly to the true migraine type, so that, in fact, the diagnosis is in question. I give briefly a few illustrative cases:

The first case is that of a healthy young Irishman,[3] twenty-four years old, who during a good part of the past ten months, and steadily for the past eleven weeks, has suffered from severe right supraorbital neuralgia, the attacks recurring regularly between eight and nine in the morning, and lasting from four to six hours. No malarial history could be obtained, and, in fact, the patient was wholly unable to assign any cause, and could not recall that the illness had been preceded by coryza. Neither could he nor his sister remember that other members of their family had had migrainoid attacks or other nervous affections. It is, however, open to question whether the testimony with regard to either of these points is fully reliable. So far as the family record is concerned, the details of the health of the parents left at home in Ireland, as had happened here, might easily be unknown to children going off at an early age to shift for themselves. As regards the previous occurrence of frontal sinus catarrh, the patient incidentally mentioned that during his attacks of pain, but only then, he was apt to have a thick discharge from the nostril of the affected side, and an examination made at the hospital by Dr. J. P. Clark, of the laryngological department, showed the presence of pus above the middle turbinate.

[1] Berlin. klin. Wochenschr., 1882, 731.
[2] Gazette méd. de Paris, 1837, 239.
[3] No. 13,729 in hospital books.

The Dr. Head test, made by passing a blunt point over the skin, showed that there was slight hyperæsthesia of the affected area, and pinching the skin confirmed the observation. There was tenderness to deep pressure over the supraorbital nerve. Large doses of quinine (15 to 20 grains), given at four o'clock in the morning, at first relieved the pain, then for a few days failed to relieve it; but by the aid of this treatment, combined with deep cauterization of the nostril and a few doses of Fowler's solution, the patient steadily and rapidly improved.

The next two cases illustrate the second group, where there is an almost strictly homologous inheritance, yet with a shadow of migraine in the background.

The first is the case of a vigorous Irish patient,[1] twenty-seven years old, one of a family of twelve healthy children. The form of the neuralgia was exactly that which has been described, with daily outbreaks, occurring in groups covering several weeks.

The first seizure had attended a sharp catarrhal attack, possibly of grippal nature, four years before his visit to the hospital; since then the illness had recurred each year, and always in the autumn until last year, when it came in August.

His mother, one brother, and one sister have all had closely similar attacks, and none of them have had typical migraine, though the sister has had headaches which are perhaps of that nature. The mother's intermittent or migrainoid neuralgia recurred for five or six years in the form of groups of attacks, each covering several weeks. The brother has had two such groups, the first of which was brought on, like his own, by an attack of grippe, while the second followed it the next year. The sister had had several groups of attacks, generally occurring in May.

The next case is that of an healthy man, fifty years old, somewhat neurasthenic, who had had typical groups of attacks, separated by intervals of several years in length, ever since his boyhood. Almost invariably, coryza, with inflammation in the frontal sinus, had been the exciting cause, though one severe attack came on in July, without apparent cause. The severity of the attacks has varied greatly, and in the severest examples there had been, besides the morning recurrence, a return of deep-seated, dull headache toward nightfall. One group of attacks was prolonged for months, and seemed to give rise to a sort of indolent neuritis of the ophthalmic division of the fifth, attended by thickening apparently of the periosteum under and above the eyebrow, which had not wholly disappeared at the end of several years. The endurance of the eye on the affected side was diminished for years, and at times scanty crops of tender papules would appear on the skin of the forehead, independently of the attacks of neuralgia. Fatigue might also bring on slight pain at any time.

[1] No. 12,931 in hospital books.

The family and personal history in this case are quite interesting. None of the patient's immediate family had suffered regularly from typical migraine, but his mother had been very subject to headaches of one or another sort, and a cousin had had migraine her life long. The patient himself had had, but only once in his life, an attack of glimmer scotoma, lasting half an hour, and not followed by headache. A brother had had a similar single attack of scotoma, followed by headache, in short, an attack of migraine.

The mother had had numerous attacks of intermittent migrainoid neuralgia, just like those of the patient, and a sister had had a single group of severe seizures of the same sort, covering a space of two weeks. These had followed a period of intense fatigue and excitement, besides a prolonged exposure to a cold wind, and the painful extraction of a large tooth. The sister's attack had been succeeded by a severe pseudo-angina pectoris, which lasted for several weeks and made walking very difficult. The same sister, when fifteen years old, had had repeated attacks of intermittent headache of the same sort with those of the patient.

Finally, I will give, briefly, three histories showing how headaches which would ordinarily and properly be called migraine may change into something more nearly resembling this intermittent migrainoid neuralgia, the sort of change to which Anstie long ago alluded.

The cases to which I wish especially to allude are the following:

The first patient is a lady,[1] now sixty-six years old, who has suffered for fourteen years or more from intermittent headaches which almost invariably affect the right side, though occasionally the left. In the early days the attacks used to recur every week or two, but of late years they have come every day, with rare exceptions. At first, also, the pain used to begin at nine or ten in the morning and go off in the course of the afternoon, but for many years the onset has been at two to four o'clock in the afternoon and the pain has continued until night, or even until midnight or one o'clock in the morning. For some hours before the attack begins she has an unnatural sensation in the legs, described as a sort of coldness, and often a sense of numbness about the lower jaw on the left side—*i. e.*, the side opposite that which is the seat of the pain. The pain mainly affects the forehead and eye, but as the attack passes away it streams down the side of the nose. There is frequently nausea during the attack, but rarely vomiting. Special tenderness over the supra-orbital nerve and hyperæsthesia of the skin are not present, and there have been no positive signs of neuritis, nor any distinct history of frontal sinus catarrh. Before these attacks began the patient used to have occasional "headaches," though not to any great extent, and her mother used to have from time to time so-called "nervous headaches" which came on in the morning and lasted for a few hours.

[1] Very kindly referred to me by Dr. R. H. Fitz.

The following case is of a similar kind:

The patient was a Hebrew woman, thirty-six years of age. Ten years or more before my examination she began to have typical migrainoid attacks, recurring every two or four weeks and lasting a single day; and these attacks continued to recur during four years. Then the neuralgiform seizures of the present type began, but still intermingled more or less with the one-day attacks. The new type is characterized by daily attacks of pain in the orbital and supra-orbital areas of the left side, occasionally the right side, coming on at ten in the morning and lasting till six in the afternoon. In the course of the past six years she has had three or four groups of these attacks, each of about four weeks' duration. One of her eight children and a cousin have "sick headaches" of some sort. The group of attacks for which she came to me had been preceded by a severe cold in the head. While she continued in attendance she received great benefit from a vigorous quinine treatment, and has remained free from pain almost constantly up to the present time, an interval of four months.

The third case is that of a gentleman of sixty-seven years, who has had, for fourteen years or more, what he himself calls "neuralgia" of the head, distinguishing it in this way from the "sick headaches" which followed him closely all the years of his middle life, finally shading off gradually into the attacks from which he now suffers. I omit the details, because there seems no doubt that the case is really one of migraine with changing type. He says that the present pain is altogether more acute in character, and more inclined to involve the rest of the face, especially at the junction of the face and the nose. The time of onset has also changed from 10 A.M. to 2 or 4 P.M. His mother suffered from similar attacks.

As regards the treatment of this intermittent headache, it is certainly true that it is amenable to quinine to a far greater extent than is the case with migraine. Certain writers have also found arsenic in large doses very useful, and I am now making observations on this point. The quinine needs to be given in large doses, fifteen to thirty grains a day, and the best plan seems to be to give the whole quantity in one or two doses about four hours before the attack is due. The local treatment of the nasal passages is also of great importance, for treatment there may indirectly improve the condition of the frontal sinuses. For the relief of the pain itself, the coal-tar remedies are not, I think, of great value, though they undoubtedly help somewhat. Cocaine instilled into the eye occasionally acts surprisingly well, and I have known galvanization of the frontal area, with a current-strength as great as could be borne, to be of service. In inveterate cases, all these remedies seem to fail, even quinine, but change of climate may

remain very useful.[1] It is doubtless true that habit comes in as a factor in perpetuating these attacks, as it does so often in nervous affections, and moral influences and changes of scene exert more effect than might be expected of them. I know of one case in which the pain ceased to recur the moment the patient started on a trip for his health. It is difficult to give a satisfactory explanation of such a phenomenon as this, but, taken in conjunction with the many other facts of kindred significance, we must conclude that pain, in spite of the prominent place which it occupies in the mind of the patient, often has a slighter hold than might be expected. The story is told of Sir John Lawrence, who was a man of remarkably strong will, that a severe facial neuralgia, to which he had been a long time a victim, disappeared when the news of the Indian mutiny was brought to him, and did not return in spite of the hardships which the situation induced. Pain is, in fact, the symptom which hypnotism and mental impressions of every sort most readily succeed in banishing.

I have spoken hitherto of the relationship between the supra-orbital neuralgia and migraine. I have, however, the notes of two cases, in one of which the second division, in the other the third division, of the fifth nerve was the seat of the main part of the pain, although in other respects the cases are evidently examples of migraine. It might be considered as unnecessary to report these cases, since it is well known, and Moebius dwells particularly on the fact, that the pain, even in typical cases of migraine, sometimes involves the face.[2] One may also infer from his remarks, with regard to an analogous point, that when the pain is felt in these areas that are usually exempt is not necessarily as an affair of irradiation in a specially severe attack, but rather because the case is of a certain type. Nevertheless, it must certainly be only in very exceptional cases that a nerve-area in the lower part of the face is so exclusively involved as in one of the instances which I shall report, while the fact that the localization seemed to be determined by the disease of the root of the canine tooth would seem to imply that the corresponding part of the nucleus of the fifth nerve

[1] Since reading this paper I have tried, with good effect in one case, the treatment by fl. ext. ergot in large doses, recommended some years ago by Dr. W. H. Thomson, of New York. See the discussion following this paper.

[2] Thomas cites a case of migraine observed by Mastboom, where the pain used to begin in the chin, and then attack successively the cheek, the vertex, the ears.

had acquired an abnormal predisposition. The case is, in outline, as follows:

The patient, now a lady of fifty-four years, had suffered at long intervals from ordinary sick headaches, but only after attacks of indigestion, as she thinks. Her mother and brother are subject to similar headaches. In the year before I saw her she had an abscess of the face set up by the disease at the root of the canine tooth on the right side, and with it suffered severely from pain in the cheek below the eye. After ten days the tooth was withdrawn, but the abscess discharged a little for several months afterward. Ever since that time she has had attacks of severe pain in the face beneath the eye, recurring at intervals of about two weeks. The pain lasts with severity for twenty-four hours, sometimes a little longer, and is often attended with nausea and vomiting. The right eye is also involved and the gums become sore. Occasionally the lower jaw becomes painful, and occasionally, also, the supra-orbital area. The pain is felt in the morning the moment she wakes, and does not pass off till nightfall. The right side of the head is occasionally affected, but not much or often. The eye is sensitive to light during the attack. The attacks come on sometimes when she has been feeling remarkably well, as happens often with ordinary attacks of migraine, but they have never been attended with visual disorders or paræsthesia.

The second case is that of a lady of thirty-two years, with a family tendency to migraine. She has herself had for some years severe headaches recurring about once a week. The pain in these headaches usually begins in the occipital area or at the vertex, and spreads over the rest of the head. It used to come in the morning, but now oftener toward night. Besides these headaches, and, she thinks, as a distinct affair from them, she has severe attacks of pain of what she calls "neuralgia" of the face and teeth. These attacks recur with more or less regularity once or twice a week, and last, generally, several days, the pain letting up toward night and coming on again more severely in the morning. About a year before her headaches began she used to have neuralgia of the leg, and this has of late been troubling her. The lower jaw becomes tender when the pain is severe, and there was at the time of my examination a small lymph-gland to be felt under the jaw, which is said to become painful and to throb during her attacks.

I have said that Anstie[1] boldly takes the position that migraine is a neuralgia of the ophthalmic division of the trigeminus, and that, like the rest of these neuralgias, it is due to degenerative processes going on in the primary nucleus of the nerve. He finds his justification for this classification in the fact that no sharp line can be drawn between the complex form of migraine, on which most of the descriptions have been based, and the localized neuralgic form. Even in the life of one

[1] Neuralgia and its Counterfeits, London, 1871.

individual the disease may change from one to the other of these types.

Moebius[1]—whose views reflect, as usual, the outcome of good observation and clear thought—regards migraine as a sign of hereditary degeneration, though capable of occurring symptomatically in connection with other cerebral disorders. He rejects the term "neurosis," as meaning nothing and only favoring a mystical dualism, and, after discussing intelligently the arguments for the localization of the disease-process in migraine, and throwing out absolutely the vasomotor theory of Du Bois Raymond, he leaves the problem of pathology as at present insoluble. Moebius does not discuss at length the relation of migraine to neuralgia, but sees no value in connecting them, and notes that the pain in the two sets of cases is very different in character. Yet, incidentally, he brings out several facts which are important for the view which I wish to enforce, such as that the pain may spread over the upper face and even the maxillary region, and that tenderness may be present over the points of exit of the supra-orbital and infra-orbital, and even the mental branches of the fifth nerve, and that herpetic eruptions may occur on the nose, etc.

Henry Head, of London,[2] whose elaborate investigations on disturbances of sensation of the skin, with special reference to referred cutaneous pains in visceral disease, have opened a new line of research in the pathology of these affections, is also of those who look upon migraine as an affection of itself. In referred headache, he says, the pain is felt in definite areas, which he has mapped out with extreme care, and the skin within these areas is hyperæsthetic to the touch of a blunt point. In migraine, he thinks, this is not the case, but the pain is deep-seated and the tenderness developed by deep pressure and by motion. The accompanying symptoms in migraine point to disorders of highly co-ordinated (cortical) functions, and Head considers it, therefore, a "neurosis *sui generis*." The experience of most writers would doubtless bear out Dr. Head's statements as to sensibility in the main, but would show, on the other hand, as I believe, that they cannot be made the basis of a classification.

Moebius says, for example, that besides the presence of nerve-trunk tenderness, the skin over the temples may be very sensitive to light

[1] Nothnagel's Specielle Path. u. Therap., Band xii., Theill. iii., v. Abtheilung.
[2] Brain, 1894. Parts lxvi. and lxvii.

pinching in attacks of migraine, and similar statements are found elsewhere.

I have very recently seen a patient with typical hereditary migraine who says that a spot in front of the vertex on the painful side is apt to be very sensitive to light pressure during the attacks, and anæsthetic after them, though the pain is referred mainly to the temple. In cases of migrainoid supra-orbital neuralgia cutaneous hyperæsthesia seems to be sometimes present, sometimes absent. In conclusion, though it may be that Anstie's designation of migraine as a form of trigeminal neuralgia is too narrow, yet signs and symptoms usually considered as indicating neuralgia are, to say the least, sometimes mixed in with those of migraine; and, on the other hand, it would be easy to call in the testimony of other writers in defense of the view that some of the symptoms usually seen only in migraine may complicate those of pure neuralgia.

My own conviction is that the study of all these great painful affections should be based on broader and deeper investigation on the *physiological* functions which the sensory nerves subserve.

The neuroses in general, and whether motor or sensory, are in my belief a sort of caricature of physiological processes, or bits of these processes cut off from their normal relations. Traces of the neuralgias are to be found presenting themselves, quasi-physiologically, in connection with or as part of the phenomena of strong emotion.

DISCUSSION.

DR. W. H. THOMSON: Some five years ago I published an article upon the treatment of periodical neuralgias with free doses of ergot, and read it before the Neurological Society of New York. Since that time I have seen a very considerable number of cases of periodical neuralgias of the supra-orbital nerve of the same kind that Dr. Putnam refers to, and have treated them successfully with this drug.

For many years I have treated migraine with the fluid extract of ergot almost exclusively. I must differ from the conclusion which I infer Dr. Putnam makes, that supra-orbital neuralgia of the periodical class is a form of migraine. I have especially asked the question whether the patients themselves have had migraine before or whether it was a family affection, and in a very small number, I do not think more than two, it had been ad-

mitted. This affection has come on with the antecedent of influenza more often than with any other antecedent.

DR. FUSSELL: I was interested in the remark that these neuralgias are scarcely ever malarial in origin. I imagine that in a very few cases have the plasmodia been searched for. Recently Dr. Johnson, now at the Soldiers' Home, Virginia, says that he has had a number of cases of supra-orbital neuralgia of periodical character in which he has found the malarial plasmodium. I shall ask him for the notes and report the cases later on.

DR. JANEWAY: I would like to ask why one should not regard these cases as probably of malarial origin if they are relieved by quinine and arsenic?

DR. J. J. PUTNAM: I remember very well Dr. Thomson's paper, which I read with great interest, and in one of these cases, which I did not report, where the neuralgia involved the second branch of the fifth nerve, I used ergot with excellent results.

With regard to the relation to migraine, I have divided these cases into three classes, in one of which I was able to trace no history of migraine, while in the others it appeared.

In regard to malaria, I do not deny that it has its effect sometimes, but I could only trace a malarial history in two cases. In some of the patients the attacks began in extreme youth and occurred at long intervals during their lives, but no other symptoms whatever of malaria showed themselves.

DR. WEIR MITCHELL: I want to say a word in regard to the chronal relations of neuralgia. It will be generally confessed that neuralgias of the fifth nerve, and especially of some branches of the fifth nerve, tend to recur about 11 o'clock in the morning. I remember many such cases. I also have noticed that people having sciatic pain do not have a return of it in the mid-morning, but about two hours after midnight. You must remember a paper by Captain Catlin, U. S. A., and myself, where a record of eleven years of traumatic neuralgic attacks is recorded. He had spells of neuralgia which came on at special hours, when they were at their worst; one was at one in the afternoon and one at four o'clock in the afternoon. I also recall to you the interesting fact observed by him that storm conditions were the governing agencies in the production of his neuralgia. He discovered that in nearly eleven years over 90 per cent. of his attacks could be traced to storms.

THE PREVALENCE AND FATALITY OF PNEUMONIA.

By CHARLES F. FOLSOM, M.D.,
of Boston.

In 1842 the State of Massachusetts commenced the registration and record of vital statistics, following almost immediately the example of England. Allowing ten years for completing details and methods and for physicians and officials to become familiar with their duties, we have from 1852 more than forty years' reports of deaths and their causes for analysis and comparison.

During this period of time the records indicate a slight increase in the total death-rate, a marked increase in the mortality from cancer, bronchitis, and diseases of the heart, kidneys, and brain; an excessively increased mortality from pneumonia; an increase from diphtheria, including, of course, croup, with three severe epidemics. The decrease in the death-rate from pulmonary consumption and from the group of infectious diseases as a whole (diarrhœal diseases, typhoid fever, cholera, whooping cough, diphtheria and croup, measles, scarlet fever, and smallpox) is very great, and it is to be expected that the decrease in diphtheria which has begun will continue. In a word, the lessened prevalence of the so-called preventable diseases is very gratifying. The increase in the total death-rate, in spite of a diminished birth-rate, and in the mortality from the diseases designated as local and constitutional, indicates that some potent causes of sickness and death are more than sufficient to counterbalance the great activity in measures to promote the health of the people which have become general throughout the State.

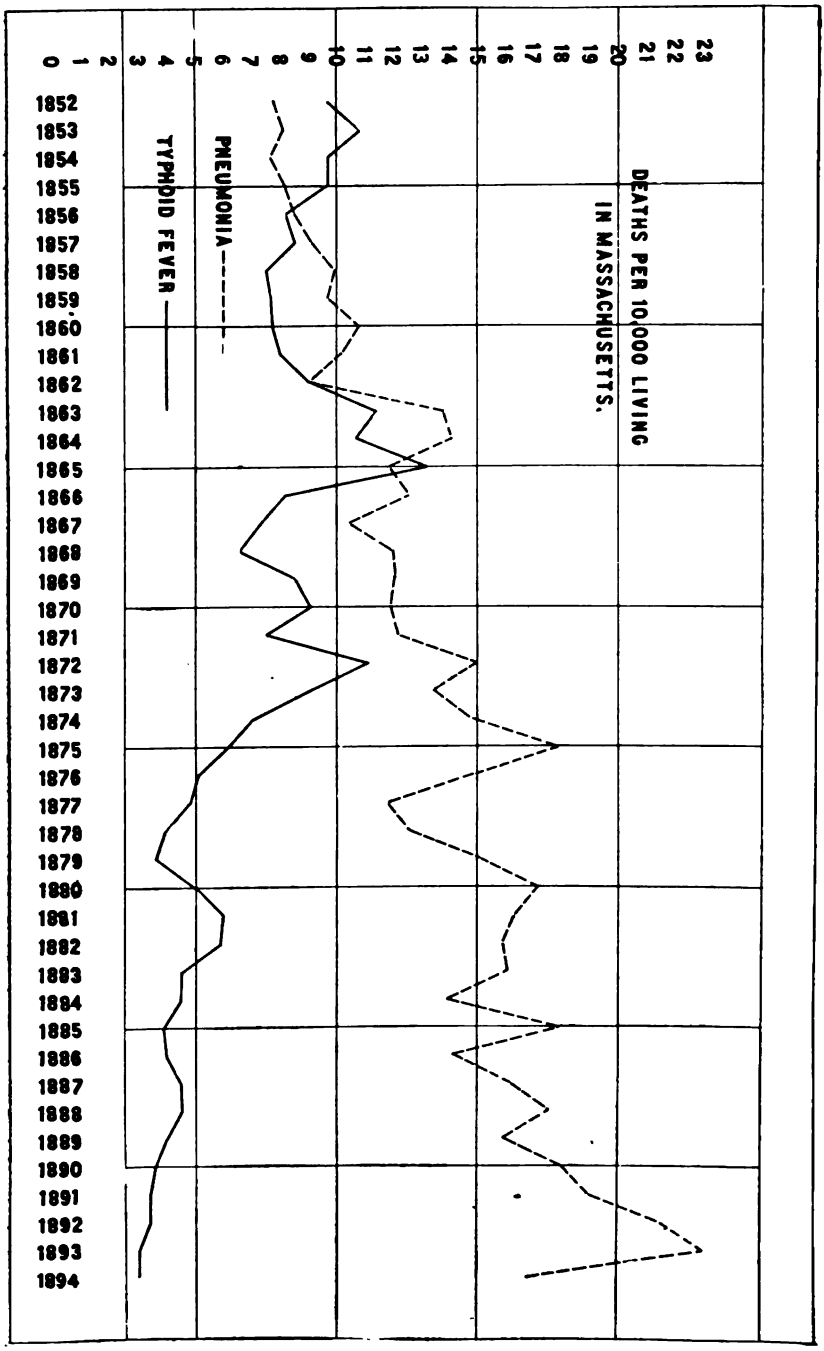
The population of Massachusetts has increased from a little over a million (1,047,520) in 1852 to two million and a half (2,500,183) in 1895. Over a million immigrants have arrived in New York and Boston in that time whose destination was given as Massachusetts, and

many thousand French Canadians swarm to and from our crowded mill-towns during periods of business activity or depression. The deterioration in the average character of the population of the State is felt otherwise than in our mortality returns, and from its aggregation in cities and towns, with their less healthful occupations than those of the country, an explanation is offered of the increased fatality from diseases, the prevention of which is to so great an extent a matter of individual intelligence and care. The fact that the "preventable diseases" have become less prevalent under such conditions is sufficient evidence of the usefulness of our boards of health. These facts and figures are most tempting for minute analysis and comparison, but however interesting such a study might be, it is not to our present purpose.

In reply to the natural question how far these statistics are exact, it can only be said that investigation shows that there are many sources of error which cannot be corrected without more attention to the matter than is at present given to it in this country. At the same time the defects are far less in Massachusetts than in the national reports, and probably less than in any other of the States. No other of our States has such full statistics for so many years. It is reasonable to suppose that part of the reduction in the annual death-rate per 10,000 living reported from consumption, for instance, from 41.1 for the five years, 1851–1855, to 23.6 for the years 1891–1893, is due to more accurate diagnosis and more careful registration, while the percentage of unknown or unreported causes of death has diminished nearly two-thirds.

One would expect the fewest mistakes in those diseases the symptoms of which are the plainest. I am satisfied that in the reported deaths from typhoid fever and pneumonia, for instance, the figures are very nearly correct for recent years, and sufficiently so for comparison earlier. General tuberculosis and appendicitis are likely to be mistaken for typhoid fever, but not in cases enough to materially affect the percentages, and the clinical picture of pneumonia is quite clear. A comparison of pneumonia with typhoid fever shows such striking results that I have placed their death-curves side by side in chart form. In 1852 pneumonia was the less fatal of the two diseases; in 1856 their lines cross in the diagram; and in the last few years the average death-rate from pneumonia has been more than five times as

CHART I.


DEATHS PER 10,000 LIVING
IN MASSACHUSETTS.
PNEUMONIA
TYPHOID FEVER
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
1852 1853 1854 1855 1856 1857 1858 1859 1860 1861 1862 1863 1864 1865 1866 1867 1868 1869 1870 1871 1872 1873 1874 1875 1876 1877 1878 1879 1880 1881 1882 1883 1884 1885 1886 1887 1888 1889 1890 1891 1892 1893 1894

great as that from typhoid fever, even after excluding the effect of the recent epidemic of influenza.

What is the inference to be drawn from this extraordinary picture? One's first thought is that typhoid fever is the type of an infectious disease, the source of which was early discovered, and the means of controlling which were easy to apply. The course of pneumonia, on the other hand, suggests to the imagination the progress of an infectious disease, which had been allowed to run rampant without any efforts to control it. But is this the whole truth or indeed a considerable part of it?

The diplococcus is one of the most pervasive, virulent, and unmanageable of the microbes. Since the reports of the infectious character of pneumonia in the Dublin Fever Hospital, more than twenty years ago, frequent statements have appeared in the medical journals attesting to its infectiousness, and the source of infection in particular cases is by no means infrequently thought about and commented upon.

I have had a mass of statistics prepared and tabulated with reference to ascertaining the conditions which govern the prevalence of pneumonia, but they prove very little that is definite and that is of value in this inquiry, so that I will not detain you with them. Harsh climates, unfavorable physical states, general ill-health, alcoholism, bad personal habits, and foul air are found by common observation to be its frequent forerunners, and the adage is that pneumonia is the friend of the aged.

Unlike typhoid fever, which is most prevalent at the ages when the powers of resistance to disease are good, pneumonia seeks out those whose resisting power, by age or otherwise, is weak or enfeebled. But it can hardly be that so great an increase in the mortality from pneumonia can be wholly due to a lower general standard of vitality and habits in the community, although the increase that has taken place in many of the chronic diseases might be fully explained in that way and through more accurate diagnosis and better, although still imperfect, registration.

In England, as I have shown by the second chart, there is a slightly diminished death-rate from pneumonia, if we exclude the effects of the recent influenza epidemic. In that country, as is well known, social and sanitary progress have gone hand in hand; the prison population

CHART II.

Death Rates from Pneumonia
per 10,000 Living.
Massachusetts
Glasgow
England

and pauperism, as well as the death-rate, have diminished, and the general condition of the people has improved.

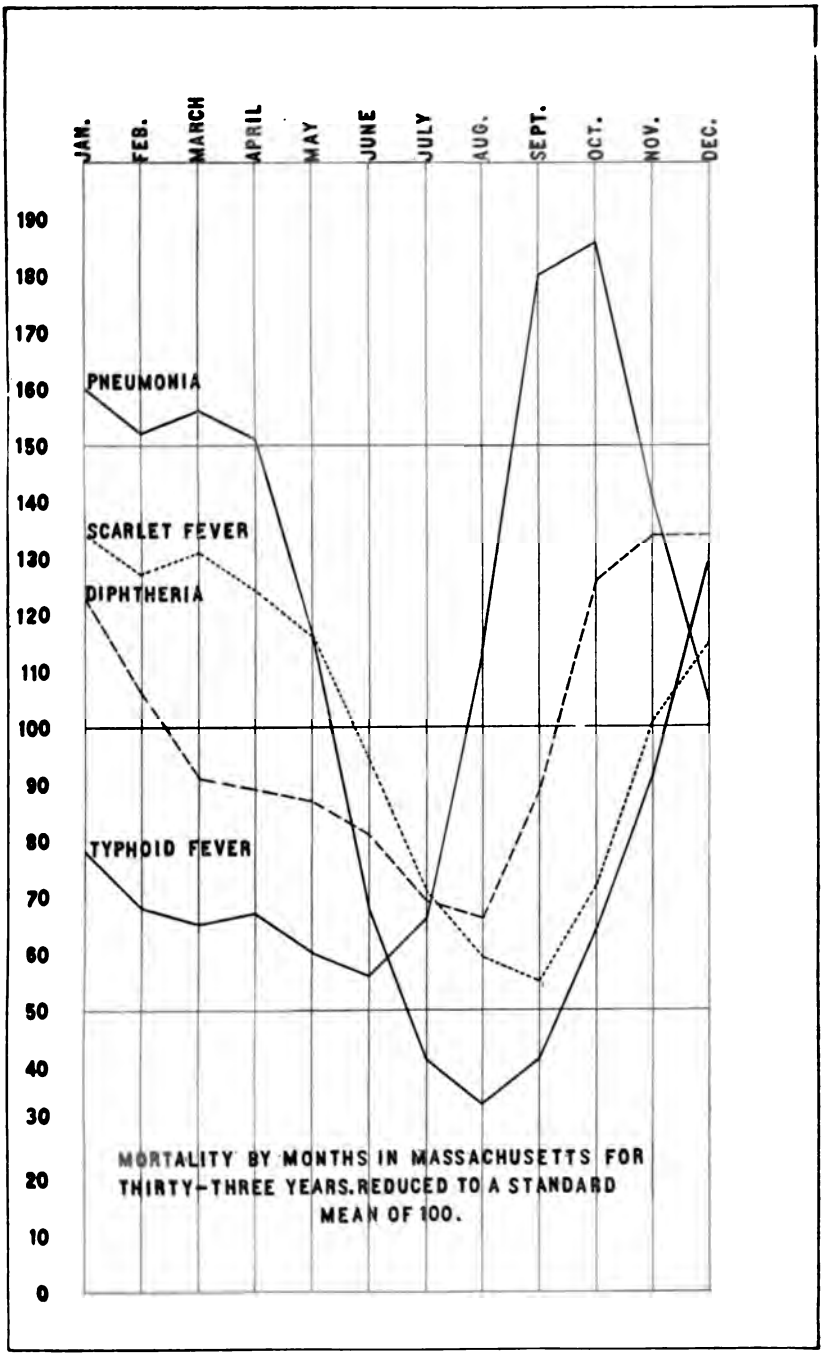
In Glasgow the death-rate from pneumonia since 1862 bears a striking resemblance to that of Massachusetts. The sanitary regulations of the city, and especially its control over infectious diseases, under Dr. Russell's able guidance, are probably the best in the world, except for its smoke-nuisance and its filth-laden atmosphere from the sewage-polluted Clyde, while its climate and fogs are even worse than ours. But even there an enormous reduction in the total death-rate has taken place, as well as from the "preventable diseases."

It is impossible with the facts now at command to say how far conditions beyond sanitary control are responsible for the excessive prevalence of pneumonia, or to what extent it is manageable as an infectious disease, if at all. But the infectious character of diphtheria was not generally admitted twenty years ago, or of influenza ten years ago. It is my very strong belief that boards of health should require notification of pneumonia to them as an infectious disease, and that after it the sick room should be disinfected as thoroughly as in diphtheria. I hope that this Association will feel disposed to vote to advise boards of health in accordance with that belief.

If it should be said that the prevalence of pneumonia follows too closely certain seasons of the year for an infectious disease, a glance at my third chart, from Dr. Abbott's statistics, shows that its curve is not very unlike those of scarlet fever and diphtheria.

As regards the treatment of pneumonia, is not the medical profession still in the habit of relying too much on medicines? That certainly seems to me a fair inference from the last paper and discussion on that subject before this Association two years ago. I find in the papers in medical journals and in the reports of discussions in medical societies an increasing tendency from year to year to trust more to hydrotherapeutics in the treatment of pneumonia and to depend less upon drugs. Personally, I have used cold sponge-baths and occasionally applications of ice for the last three years in my hospital wards in every case of pneumonia, except those absolutely *in extremis*. As the months of my service are before the time of greatest prevalence of pneumonia, my cases are not yet enough for tabulation and generalization. I am satisfied that life may be saved by that means, and I am sure that thereby delirium is quieted, pain is relieved, cough

CHART III.


JAN.
FEB.
MARCH
APRIL
MAY
JUNE
JULY
AUG.
SEPT.
OCT.
NOV.
DEC.
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PNEUMONIA
SCARLET FEVER
DIPHTHERIA
TYPHOID FEVER
MORTALITY BY MONTHS IN MASSACHUSETTS FOR THIRTY-THREE YEARS. REDUCED TO A STANDARD MEAN OF 100.

is eased, and sleep is produced without the necessity of resorting to drugs. That the tonic effect of cold sponge-baths is fully as great in pneumonia as in typhoid fever is fully borne out by my experience, and I have never seen any ill effects from them. The greatest number of baths that I have used in a single case has been twenty-five, and every patient without exception has expressed a feeling of comfort from them and of liking them, unlike my typhoid patients, a large proportion of whom complain bitterly of their cold baths.

TRICUSPID STENOSIS.

By GEORGE DOCK, M.D.,
OF ANN ARBOR, MICHIGAN.

HUGH P., American, white, aged nineteen years, was admitted to the University Hospital as a surgical patient March 20, 1893, but transferred next day to the medical ward.

The father is living and well. The mother died of phthisis after influenza, and is said to have had a "double valvular lesion." Otherwise the family history is negative. As a child the patient was never well, but was weak and puny. At an early age had measles and whooping-cough. At eight years had a mild attack of chorea, lasting about a month. At twelve years had scarlatina. Has had influenza once; never had rheumatism. Before the winter of 1892–93 was always able to be about, though not strong; had frequent headache. Some time in 1892 it was first noticed that the patient's face was "blue." There is no history of cough or shortness of breath.

Present condition. March 21, 1893. Frame small and undeveloped, resembling that of a lad four or five years younger. Height 5 feet 4 inches, weight 121 pounds. Muscles small, but firm; panniculus thin. The skin is sallow, not jaundiced; there is marked cyanosis and congestion of the ears, lips, cheeks and nose. Temperature 98° F. The hands are cool and cyanosed. The toes of both feet are blue, cold; there is slight œdema of the feet and ankles. On the tips of the toes are superficial blebs, some of which have ruptured. This condition came on after exposure to cold hardly sufficient to affect a healthy person.

The tongue is slightly swollen, thin white-coated. Stomach negative; stools regular.

The thorax is long, narrow, slightly pigeon-breasted. Respiration chiefly diaphragmatic; 20. Examination of lungs negative.

There is a marked pulsation in the second, third, fourth and fifth interspaces from the left edge of the sternum to the left anterior axillary line. On the right side there is a plain pulsation in the third interspace, less marked but distinct in the fourth and fifth. The apex-beat is strongest in the fifth interspace midway between the nipple and anterior axillary line. Inside the left nipple-line in the third, fourth, and fifth interspaces is a pre-

systolic thrill, coarse and strong, most marked in the fourth interspace in the parasternal line.

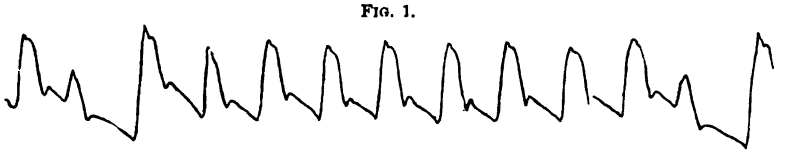
The absolute heart-dulness begins on the third rib, to the left of the sternum, extends to the left of the nipple-line in the fifth interspace, and one finger-breadth to the right of the sternum from the third rib to the line of liver-dulness. The sternum gives a dull note within this area.

In the apex region is a loud blowing diastolic murmur, loudest at the end, just before the apex-beat. It is best heard in the third and fourth interspaces, just within the nipple-line, is faintly transmitted into the axilla, up to the aortic and pulmonary areas but not higher; faintly heard in the back. The first sound is loud and flapping at the apex, faint at the aortic cartilage. The pulmonary second sound is accentuated.

The heart's action is very irregular, occasionally asystole being followed by several strong quick beats. There is a strong pulsation in all the peripheral arteries, the head moving with each beat.

Radial pulse 90, irregular in force and rhythm; moderately full, strong, rather quick (see tracing).

FIG. 1.



The abdomen is above the level of the ribs; there is epigastric pulsation; palpation of abdomen negative.

Liver-dulness begins in the fifth interspace in the right nipple-line, extends one finger-breadth below the ribs. There is tenderness on pressure over the liver; no pulsation.

The splenic dulness is large, but the spleen cannot be felt.

Urine examination. 350 c.c.; specific gravity, 1023; acid; dark yellow; slightly turbid. A small amount of albumin; no sugar; a few leucocytes and hyaline casts.

After admission to the ward a cough began, with scant expectoration, tough, mucous, and bloody, containing alveolar cells. A few râles were heard over the bases. Cyanosis of the face and a trace of icterus were present for a few days and then disappeared.

In a clinical lecture, March 24, 1893, the case was presented as one of mitral stenosis with some other lesion, besides the probable aortic and mitral regurgitation. It was held that there was either a congenital anomaly, perhaps a patent foramen ovale, or tricuspid disease, though the difficulty of demonstrating the former and the absence of positive evidence of the latter were explained. The probability of the

existence of tricuspid stenosis, as explaining the cyanosis, was considered then, as at many times later, but given up for want of evidence in the form of a murmur, and a congenital anomaly was considered more probable on account of the history. This reasoning proved incorrect, as will be shown later. The further history of the case can be best made clear by describing in brief the course of certain symptoms.

By the end of a week after admission, with rest in bed, the heart became regular and long remained so. Afterward strychnine and digitalis were given in small doses. The toes healed, the cyanosis lessened, but did not disappear.

After remaining away for several months P. returned as an out-patient October 6, 1893. He was greatly cyanosed; there was slight œdema of the ankles; the hands were cold. The pulsation in the cardiac area was more extensive, reaching to the seventh interspace in the mid-axillary line. The thrill was still to be felt from the third to the fifth interspace and from the left edge of the sternum to an inch outside of the nipple. There was also a thrill in the second interspace, to the right and left of the sternum, which was of slightly different time from the former, being felt earlier and not lasting so long as the other. The absolute dulness extending a finger-breadth further to the right and left than before. The presystolic murmur was heard as before. The first sound at the apex was loud and sharp. The murmur had its point of greatest intensity just within the nipple, was transmitted to the left and above, but not heard inside of the parasternal line. The aortic second sound was not audible. There was no systolic murmur anywhere; no positive venous pulse. The pulse was small, moderately quick. No peripheral pulsations.

There was no cough or expectoration; no signs in the lungs.

The cyanosis and œdema improved; the pulse became stronger and fuller (see Fig. 2). The apex was gradually withdrawn to the fifth interspace

FIG. 2.

just within the nipple-line (November 3d). The dulness to the right unchanged. The murmur was as before.

In December another period of loss of compensation came on and on the 11th the patient was again admitted. The physical signs were the same as at previous examinations, but on December 31st a soft systolic murmur was heard at the apex and remained present more or less constantly after that. This was looked on as being due to mitral regurgitation, long supposed to be present without a murmur.

On January 2, 1894, and the following day an additional murmur was heard; a high-pitched, almost musical murmur heard at the tip of the sternum, systolic in time.

From this time no radical change took place in the auscultatory conditions. The diagnosis was mitral double lesion, aortic insufficiency, and tricuspid regurgitation.

The murmurs mentioned remained about the same, except at times when the heart was very weak. Although the case was frequently examined no other murmurs were heard. Besides being examined by numerous classes of medical students, a number of physicians saw the patient at various times, but nothing was added to the idea expressed above.

The cyanosis remained more or less constant after December, 1893. It was never marked, except when the patient became cold. True cyanosis was present only on the face. The hands and feet were usually cold and congested. After the first attack there were no other nutritive disturbances in the skin until shortly before death.

When first admitted there was slight œdema of the ankles. This recurred from time to time, when loss of compensation was otherwise marked, but was never very severe. In December, 1893, the patient lay for a long time on his right side on account of pain, and then had considerable œdema of the right side of the face. During the last few months œdema was slight or absent.

As this lessened ascites became more prominent as a symptom. It was first observed in May, 1893, but was not marked and soon subsided. In October the liver extended three finger-breadths below the margin of the ribs; the edge was hard and smooth. There was no ascites at that time. On December 11th, when the liver was about the same size and sensitive, ascites came on. The abdomen was much distended and gave all the signs of free fluid. The ascites lessened, however, while under treatment, but again increased, so that paracentesis was necessary on March 8, 1894, when 5850 c.cm. were removed. The fluid was clear, yellow, sp. gr. 1012, and had all chemical characteristics of ordinary ascitic fluid.

The fluid reaccumulated rapidly, so that tapping was necessary about every two or three weeks, quantities of 7 to 12 litres being removed. Altogether 96,850 c.cm. were taken away between March 8th and September 1st in ten operations.

The liver grew smaller gradually, so that by the end of May it could not be felt below the ribs.

As an evidence of the arterial anæmia the excretion of urine was always extremely scanty. Up to the end of 1893 quantities as large as one litre in twenty-four hours were usual. After that with increasing dropsical accumulation the excretion fell to about 300 c.cm. daily. The urine contained albumin, often hyaline casts, occasionally blood.

No drug had any marked influence on the excretion of urine. Digitalis, digitalinum verum, diuretin, and many other diuretics of various kinds were given with either temporary or no effect.

During the last year diarrhœa, vomiting, pain in the stomach region, at times vomiting of blood, gave evidence of gastro-intestinal congestion and had much to do with exhausting the patient.

During the last few months the temperature showed the tendency to drop below the normal, and for two months before death remained below 98°, except on four days, and for most of the time was about 96°.

It is a matter of regret that the notes on examinations of the blood, made from time to time, have been lost. There was at all events a high corpuscle-count.

Death occurred September 15, 1894.

The autopsy was made seven hours after death. From the notes I extract the following: Slight rigor mortis; cyanosis pronounced on face, hands, feet, and legs. The skin in general sallow. No œdema. The subcutaneous tissue wasted; muscles, especially those of thorax and abdomen, extremely wasted. The abdomen contains five litres of fluid, like that removed during life. The peritoneum is slightly opaque, but not thickened. The serosa of the intestine is dark red, the vessels distended.

FIG. 3.

There are 400 c.cm. of clear yellow fluid in the right, 200 c.cm. in the left pleural cavity.

The lungs, partially collapsed, are anæmic, slightly pigmented, show slight œdema and a trace of hypostatic congestion. There are no adhesions; the right apex shows small scars.

The pericardium contains 200 c.cm. of clear fluid. There is a recent adhesion over the right auricle, occupying a space the size of a silver dollar. The heart extends 4 cm. from the middle line in the second right intercostal space, and to the fifth interspace in the left anterior-axillary line. The larger part of the heart is formed by the auricles.

The heart was hardened distended; before alcohol-hardening it gave the following measurements:

Width across auricles, 14 cm. Depth of auricles (antero-posterior), 10 cm. Width at ring, 12 cm. Septum of the ventricles, length, 8 cm. After hardening the heart became 1 cm. smaller in all the principal diameters. The muscle measures (after hardening): At the middle of the ventricular septum, 8 mm. Anterior part of left ventricle, 10 mm. Left side of left ventricle, 12 mm. Posterior wall of left ventricle, 13 mm. The papillary muscles of the left ventricle are small; the posterior measures 12 by 4 mm.; the anterior is smaller, narrow, and irregular. The wall of the right ventricle, anterior, 2.5 mm. Right side of right ventricle, 2 mm. Posterior wall of right ventricle, 4 mm. The anterior papillary muscle 6 by 2 mm. in thickness. The left ventricle contains a large dark-red clot.

The mitral orifice is elliptical, 10 by 5 mm., the long axis antero-posterior. The margin shows a few firm nodules. The mitral flaps are nodular and calcified.

The aortic orifice is of triangular outline, 10 mm. long, 18 cm. across. The aortic sinus is short.

FIG. 4.

The right ventricle contains a mixed clot, continuous with that in the auricle. The auriculo-ventricular orifice is oval, 13 by 10 mm. in diameter.

The right auricle measures 6.5 cm. from side to side, 8 cm. from before backward, 9.5 cm. from the top to the orifice, or 7.5 cm. from the top to the level of insertion of the valves. The flaps form a shallow concave curtain. The appendix of the right auricle is filled with a dark, firm, adherent thrombus, 9 by 7 cm. on section, extending into the cavity of the auricle, with a long, fibrinous string passing through the orifice. The recesses in the wall of the auricle contain similar smaller thrombi. The walls of the auricle are very thin, and in many places there are areas as much as 5 cm. wide, between the long bands of muscular fibres, composed only of the two serous layers.

The left auricle is 6 cm. wide, 6 cm. deep, and 6 cm. high, or, to the orifice of the mitral valve, 8 cm. The appendix is long and twisted, and contains a thrombus. The foramen ovale is 6 by 2 mm. in diameter, opening as a narrow passage between the layers of the septum.

The coronary vein is 1 cm. in diameter; the coronary arteries very narrow.

The aorta is 18 mm. in diameter. The valves are thick, rigid, calcified. The pulmonary artery is 25 mm. in diameter; the valves thick, but not rigid.

The spleen is 10 cm. long, 7.5 cm. wide, 3 to 5 cm. thick. It is hard; the capsule is smooth and thick. Section of the spleen is dark red, anæmic; the fibrous tissue is increased.

The left kidney measures 9.5 by 3.5 cm. The capsule is smooth, not adherent. Section is bloody; the cortex, 6 mm. wide, is granular and red; the pyramids only slightly cyanotic, the tissue firm; the epithelium not cloudy.

The right kidney is 10.5 by 5 by 5 cm., the cortex 8 mm. wide, otherwise as the left.

The supra-renal bodies, ureters, and bladder are normal.

The stomach is small; the mucous membrane rather thick, pigmented; the cardiac and œsophageal veins not dilated.

The intestine shows slight congestion in the upper part; the lymphoid tissue pigmented; otherwise no change.

The liver is small; weighs 1240 grammes. The edges are rounded; the capsule smooth, thick, opaque. The section is bloody, showing areas of dirty-yellow color in lobular arrangement, surrounding areas of dark-purple or chocolate color; the latter sink below the level of the yellow areas after section. In various parts, especially near the capsule, are areas of connective tissue, some of them stellate, others irregular in outline, of considerable extent.

Gall-bladder small; ducts normal.

Mesenteric glands enlarged.

Pancreas normal.

This case illustrates in many respects the characteristics of tricuspid stenosis. This has within the last few years received so much attention, and especially at the hands of B. Fenwick, Leudet, Shattuck, and Ashton and Stewart has been so fully elucidated, that it is unnecessary to make an extensive investigation here. The sex of the patient is against the rule, but the fact appears that the patient lived under the conditions claimed by Fenwick as obtaining in women.

As regards the history, the question of etiology is especially important on account of the presence of the patent foramen ovale. It would seem that this must have been congenital, for, although the foramen may be forced by differences of pressure in post-infant life, the form of the orifice here seems to indicate a congenital lesion. It does not seem to me that the patency was associated with other congenital lesion—as, for example, a right-sided endocarditis—otherwise cyanosis would have been likely to come on much earlier than it did.

The chorea would seem the most probable cause of the endocarditis, beginning in the mitral valve, and from this the disease gradually involved the aortic and tricuspid valves, perhaps assisted by infections in the subsequent diseases.

With regard to the physical signs, the conditions were not peculiar. As in the majority of such cases, an accurate diagnosis was not made, though the condition was suspected and its probability often discussed at the bedside. In another case I think I should be able to make a correct diagnosis, yet at the time the supposition of a congenital lesion, which was actually present, seemed sufficient to explain the departure from the usual picture of valvular disease.

Notwithstanding the numerous examinations made, at no time was there a positive venous pulse in the neck. Liver-pulse was likewise absent. On the other hand, the changes which actually took place in the liver were of great clinical importance. During life the various stages of congestion and atrophy with induration were definitely shown by the symptoms.

The macroscopic characteristics of the liver are marked. The microscopic changes need only a few more words. The conditions vary widely in the outer part, to the depth of about a centimetre, and the inner part. The latter represents the earlier stages of the process. Here the capillaries in the central zones of the acini are dilated. The central vein usually does not show marked dilatation, nor does it reveal evidences of thickening in the wall. The extent of the dilatation varies greatly in different areas. In some acini the process is barely indicated. In others the capillaries are two or three times the normal width. In others, there is an actual cavernous degeneration. The liver-beams appear as narrow strands, the cells small and deeply pigmented, between blood channels sometimes half the width of a normal acinus. In some parts of the organ there are areas of considerable size affected in this way.

In the inner part of the liver the cells are often atrophic, pigmented, sometimes fatty-degenerated. In many places, but not uniformly, there is an excess of connective tissue. This is found especially along or near the branches of the hepatic vein. Sometimes it passes from a central vein in rays or strands. This tissue is for the most part soft-looking, rich in nuclei. It contains vessels of various sizes and degrees of development, and sometimes considerable bile pigment.

In the inner part there is also an increase of connective tissue around the portal vessels. This is very irregular in distribution and does not form an important part of the process.

The outer, firmer, zone of the liver evidently shows a late stage of the

change. The external capsule is thick and sclerotic. Immediately beneath this there is a network of connective tissue containing, at somewhat regular intervals, the remains of portal areas which can be recognized as such, though the various vessels are small. At times small areas of liver tissue, the cells usually small and pigmented, may be seen. In other parts are small cavernous areas, usually without liver-beams. In the dense tissue hepatic veins with thickened walls are not uncommon; often these vessels are considerably dilated. The dense network of connective tissue seems to follow the portal divisions, though the thickened central veins have a part in it. It would seem that the outer part was the first to undergo capillary dilatation, atrophy, and subsequent sclerosis. The various factors in the process, other than those due to the obstructed circulation, such as toxic agencies, need not be discussed at present.

ON THE EXCEPTIONAL EFFECTS OF BROMIDES.

By S. WEIR MITCHELL, M.D., LL.D.,
OF PHILADELPHIA.

THE ordinary or excessive use of bromides sometimes occasions symptoms which are familiar in their milder expressions, but which, I am sure, are rarely seen in their more interesting and aggravated forms; or, if so seen, are not always suspected to be due to the use of these salts. In certain people these rare and extreme results are not due alone to the bromides. The prodromes, or the consequences, of an epileptic fit may, because of the bromides, be intensified even in those whose attacks are being lessened in number. This, I am sure, I have seen, and I have several times had remarked by the nurse, or the patient's relatives, that the irritability so often seen before or after a fit was the worse for the bromides. Menstruation admits of the same comment, the curve of the irritability or melancholy being sometimes higher at this time in epileptics under free use of bromides. Trauma affecting the brain, as from fractures, or internally caused lesions, may give us to see excessive displays of bromic influences causing bad temper, suicidal or homicidal tendencies, temporary delusions. Cases of necrotic changes, from emboli or thrombi, may be thus responsible for unusual bromic effects; but it is to be remembered that of all the mental symptoms evolved by bromides irritability alone is common, and the rest exceptionally rare. Most people take the usual doses of bromides without other ill effects than acne, roughened skin, and excess of urine, especially if it be the lithia salt which is used.

Dr. Da Costa calls my attention to the fact that, although ordinarily these salts do not disturb the circulation, they may do so when certain functional failure of heart-force exists. He says: "I have been struck with the fact of the depressing, and even serious, effects

in those who have weak hearts, and especially the form of cardiac weakness designated as chronic cardiac asthenia. The action of the heart becomes distinctly feebler under the continued decided use of bromides, and sweats are apt to break out; all of which symptoms disappear when their employment is discontinued." In a few patients even moderate doses occasion the paretic symptoms always seen soon or late in such as are using immoderate amounts of these agents.

One of the earlier physical effects, as Dr. Rudisch, of New York, has pointed out to me, is a tendency to ptosis; the lids fall more than is common, the eye space is narrowed. Next comes increasing paresis of all the limbs, even to inability to walk, and this feebleness may be so much more notable on one side as to look like a hemiplegic condition. As the weakness increases the spinal muscles are affected, and, for a time, the spinal curves are altered, and to sit erect is difficult. The pupils are moderately dilated. On the side of the mind, there is failing memory, difficulty as to fixation of attention, hebetude, and so, at last, a general condition like that of some partial imbeciles. With paresis there may be indifference as to body habits, or the sphincters may be so relaxed that the feces or urine cannot be retained. This extreme state of things we rarely see, but now and then accident or reckless lay use of the drug in question gives an opportunity of the utmost interest.

I saw, in 1887, a child, of fifteen years, long subject to Jacksonian epilepsy ending in general convulsions. The father, an apothecary, determined to suppress the disease by the use of bromides. "If," he said, "a drachm a day holds the fits in check, two or more should put an end to them." On this theory he increased the doses to 150 grains a day. After ten days of this treatment I saw the child. She was unable to stand, and when seated her head dropped forward, and she remained, as the mother said, "all of a heap." The eyes were a third open, the pupils large, the sphincters relaxed, and the saliva flowed from the fallen jaw. As to her mind, she was quite imbecile, hard to arouse, and stupidly indifferent. The general convulsions had ceased, but the lesser fits were quadrupled in number—a not rare incident. A few days without bromides entirely restored her to normal conditions of body and mind, and the state of partial idiocy was exchanged for normal condition of rather unusual intelligence.

I saw, many years ago, and at nearly the same time, in my wards at

the Infirmary for Nervous Diseases, two children, each of whom took daily, owing to a mistake of the nurse, nearly 100 grains a day of lithium bromide. I had just introduced this bromide into medicine, and was giving it to all the cases to which previously potassium bromide had been given. These two children were between ten and thirteen years of age, and were both cases of mild epilepsy. In a few days both were brought into a condition of extraordinary feebleness of mind and body. Memory was impaired in both, so that one forgot the letters of the alphabet, and, of course, could no longer read; the other had some curious confusion as to the time of events—misdating them. My visit, she declared to the nurse, was made the day before, although I had just left her bedside. Her dinner, she said, had been taken early that day, and yet the tray was still before her. Her memory of events was, if not sharp, at least such as to enable her to recall all things of recent occurrence, but she never succeeded in relating them correctly to the time of week or day. This interesting state of altered memory was naturally of brief duration, passing away within two days after the bromides were withdrawn. In both of these cases the weakness was very great; both could stand, swaying somewhat, but neither could walk. When this was attempted they both fell to the left, the left leg being manifestly worse than the right, as is often the case in drunkards, some of whom are often more drunk on the left side than on the right.

There are a few cases in which bromides (sixty grains daily) occasion at first a mere depression of spirits, as we say, which, save in rare cases, is not lasting. Now and then we find people who do not bear any effective dose of bromides, and who are in a state of moderate melancholia so long as we give the drug. In a still smaller number the effect of each dose is felt in a deepening of the sadness. In exceptional cases this influence may rise to the grade of danger and occasion suicidal impulses. Of this I saw, a few years ago, a strange example.

A lady, the wife of a physician, consulted me as to long-continued sciatica. She had had, four years before, three severe convulsions while nursing her last child. Ever since she had continued to take sixty grains daily of mixed bromides, being in constant dread of another attack. The medicine did not trouble her, nor was there the least sign of acne. She was, at this time, about forty-seven years old,

and was becoming slightly irregular as to the time of menstruation. Within a year she had begun to be intensely depressed at, before, or a few days after the menstrual onset. Of late this recurrent melancholy was such as that for four days at the beginning of the flow she had suicidal impulses. The mid-interval was, she assured me, free from this distress of mind. About this time she reluctantly confessed to the constant use of bromides, which I induced her to abandon. To her surprise, the next period, which came two weeks after disuse of the drug, was nearly free from melancholy, and the next entirely so. These abrupt endings of any type of melancholy are rare, but still clinically possible. However this may be, the melancholia was seen no more for a year. Then, while suffering from temporary loss of sleep, she was given for three or four days ninety grains a day of some bromide. It plunged her into deep melancholy, although she was not at the time menstruating. The drug was abandoned and the symptom went with it. The dose was larger than that which with the menstrual crisis had before seemed competent to occasion melancholy.

I have seen other examples of grave melancholy from bromides in males, as well as in females, and in one notable case of bromic habit a very intense melancholia with a face so sombre as not easily to be forgotten.

It is far more common to see irritability of temper occasioned by bromides. In old epileptics it is laid to the score of the disease, but that it is not always of this parentage is a matter worth remembering in extreme cases. I know of several cases of old epilepsy in which the families of the sufferers came to understand that the bromides were the causative factors in giving rise to states of irritability, abruptness of manner, or peevishness in persons by nature gentle and amiable. When the outbreaks of temper were extreme in these cases, it was customary to stop the bromide for a week, and to take the risks of an attack for a time at least. Last year I saw in my clinic service two young epileptics (both boys) who were what their parents termed "ugly-tempered" while using bromides, apt to break things, short of temper, "sudden-like," was the description given one of them. This tendency to destructive outbreaks with unrestrained violence of temper does, in a few people, rise to the danger-line.

Ten years ago I was consulted as to an epileptic lad, the son of a physician, who could not take bromides a week without becoming

homicidal. I disbelieved the accounts given me, or rather thought some mistake might have been readily made in an epileptic as to the cause of these outbreaks. I was reluctantly permitted to give forty-five grains a day of potassium bromide. The experiment came near to resulting in a tragedy, and I became amply satisfied.

Another case of like nature, also an epileptic, was seen in a young and sturdy farmer. All use of bromides had to be laid aside. If he took them he began within a week to be both irritable and depressed; later, the melancholy lessened and the irritability rose to conditions of unrestrained anger, often upon the slightest provocation. If the bromides were still further pushed, this man grew sullen and dangerously homicidal.

I saw a case much like this a few years ago while acting as consultant to the City Hospital Insane Wards. The sufferer was a partial dement from years of epilepsy, but under bromides became violent and dangerous. No doubt the asylums could tell us of other and similar cases.

My friend, Dr. Draper, permits me to relate a case within his experience. A lady in middle life, ill in Paris, was seen by Charcot and Brown-Séquard on account of some disturbance of general health and loss of sleep. Very soon she became excited and soon after so wildly maniacal as to give rise to the gravest prognostications. Her friends in this country heard by cable of her state. Dr. Draper promptly asked if she were taking bromides. She had been, but they had been laid aside by Charcot's suggestion. In a few days she was well. Dr. Draper's previous experience of the case enabled him to suggest the cause of this sudden mania.

Hitherto I have spoken of these unusual effects of bromides in the healthy, or in those who have no more pronounced lesions than the ordinary types of epilepsy present. Occasionally persons who have had emboli, or destructive necrotic processes about clots, or from thrombosis, or those who have had traumas show extraordinary susceptibility to bromic influences of unusual nature.

The worst case of almost sudden bromic toxication, I saw years ago in consultation, A young man had rheumatism, heart-disease, and multiple emboli, one in the middle cerebral artery on the right side. After a perilous rise of temperature it fell to 100° F. for two weeks, with increasing evidences of destructive irritative changes in

the brain. At this time one drachm of potassium bromide used daily for three days resulted in acute mania. It was laid aside, and only when used anew had I the suspicion that my drug was to blame. A third experiment satisfied me.

I have seen but of late an intelligent and able engineer, who was so injured during a railway accident as to become palsied on the right side and comatose, until relieved by trephining and the removal of depressed bone and a small spicula of bone which penetrated the skull about one-fourth of an inch at the anterior parietal margin. A skilful operation was followed by swift and entire recovery. Living at a great altitude, and subject always to neuralgic headaches, he now began to sleep badly and to have severe headaches. For this insomnia he took without orders a bottle or two a day of some proprietary stuff known as bromo-seltzer. The amount thus taken could not have exceeded eighty grains a day. His very competent physician at this time, learning of the habit, told him to give up the bromo-seltzer, and later, under the impression that he had obeyed orders, prescribed the use at bedtime of a small dose of chloral with thirty grains of potassium bromide. Meanwhile, with increasing irritability of temper came lessened capacity to manage affairs. Then at times he became violent and threatening and at last even dangerous. It was thought well that he should live at a lower elevation, and with this in view he was sent hither and put under the care of Dr. John K. Mitchell. To get a full knowledge of his condition all drugs were laid aside, and we then learned that despite his physician's orders he had continued to take bromides in excess. A week after he ceased to take them he was freed from all the distressing symptoms which we and others naturally put to the credit of the cerebral lesion. He was no longer irritable; he became, as he was before the accident, amiable and merry, and has been able to write long letters and to discuss and decide matters of business. Those who know him best can see little difference between his present condition and that with which they have been familiar in past years. It should be said that this excitability could be easily and more quickly awakened by the smallest amount of alcoholic stimulus or any large use of tobacco.

Eccheverria was the first, I believe, to call attention to the fact that bromides are competent to give rise to suicidal and homicidal impulses.

DISCUSSION.

DR. JANEWAY: I have had my own mind drawn to this matter in several directions. In the first place I have seen a number of deaths from bromide, and those deaths followed by autopsies in which there was no discoverable lesion, and nothing to explain them other than the enormous use of bromide. I have known of five cases of that kind. Two were at a time when bromide was being given in excessive doses. They sank into a condition of apathy from which they did not rouse. I saw three autopsies in the five cases I have mentioned. In one case an ounce a day of bromide of potassium was used. In another case six drachms, and in another case only three drachms, but these doses were kept up in one case for nearly a month, in another case for some three weeks, and descending doses were then used. The coroners of New York have told me of two additional cases.

There is another drug, bromo-soda, which is frequently taken by alcoholics when recovering from their sprees. I have known of two cases of supposed general paresis due to bromide. In one case an expert had pronounced the condition general paresis and advised the patient's removal to an asylum. The patient recovered in a few days, and the physicians could not account for it until he had had another attack, when it was found that he had used bromo-soda.

A gentleman came to me from Rhode Island with a condition which made me think that he had general paresis. Remembering this other case, I asked him if he were using bromo-soda, and found that he was taking six bottles a day. He told me that the fizz was good, and he took it on account of the effervescence. The sparkle seemed something like what he had been in the habit of having.

I mention these cases to call the attention of physicians to the fact that there is a disposition on the part of alcoholics to take something of this kind and sometimes in very large quantities, which may bring on conditions simulating dementia from alcoholism and general paresis.

Dr. Mitchell mentions instances of bromic toxication in disease. I saw two years ago a physician recovering from typhoid. Because of his marked melancholia and suicidal tendencies I cross-questioned him about the use of drugs. I had the slips brought to me, and found he was using bromide in considerable quantity, because the nurses had put in additional doses. The mental condition seemed to be due to bromide with chloral added. I recommended it to be abandoned, and in one week the man had made a marked improvement. I have no doubt that in typhoid fever and in other conditions we find at times symptoms that are dependent upon the drugs we give, bromide and chloral among them. Not only that, but occasionally we meet with a case like the one I have in mind of a merchant having severe headaches, a business man, bright and active. He would take twenty to thirty grains of

bromide of potassium or sodium at night. He assured me that whenever he did so he was utterly unable to do business the next day. His memory became treacherous. Time and again he repeated the experiment. This is an illustration that a very moderate dose of bromide in susceptible people will produce altogether unexpected results.

This is a very valuable contribution of Dr. Mitchell's, because it calls the attention of the profession to the fact that the effects of drugs should be carefully scrutinized, and the symptoms of drugs be separated from the symptoms of the disease.

DR. HARE: In this connection it is well to remember the depressing influence exercised upon the nervous system and upon the vital functions of the heart and respiration by the potassium salts. The studies of Sydney Ringer and other investigators have shown that potassium itself is one of the most depressing poisons that we have. Even such mild potassium salts as the citrate or acetate in large doses will produce considerable depression. I have in mind a child of six or eight years receiving as much as thirty or forty grains of citrate of potassium for several days. After three or four days he passed into a condition of depression and collapse which was exceedingly alarming, and not until the potassium citrate was stopped did signs of improvement occur.

I cannot help wondering whether in a certain number of cases, such as Dr. Mitchell has reported, the base with which the bromine is combined has not had quite as much to do with producing some disturbance of the nervous system as the bromide itself. Of course I recognize the fact that Dr. Mitchell has reported a number of cases in which the bromine must have had this influence, because he has used bromide of lithium and other salts. I do not think that the profession recognizes the fact that with the bromide influence they often get this positive depressant influence of the potassium salts, and I often wondered why the profession seemed so wedded to the use of bromide of potassium instead of using the bromide of sodium which is devoid of the depressant influence which the former possesses. This is an advantage of the bromide of lithium over the bromide of potassium. The lithium salts are, however, more irritating to the stomach than those of sodium.

In regard to those cases mentioned by Dr. Janeway, who were taking combinations which are practically proprietary, such as bromo-seltzer and bromo-soda, it is a question whether the mental disturbance was not largely due to the caffein which they contain. It has been shown that when large doses of caffein are administered patients are very apt to develop symptoms of "caffein craziness." I have in mind two patients, one of whom took fifteen grains of citrate of caffein in each twenty-four hours, and in the course of three or four days developed distinct suicidal tendencies. In another case where large doses of citrate of caffein were taken, the patient committed suicide by jumping out of the window of the hospital ward. In these cases where they often take

caffein we cannot think the entire result is due to the influence of the bromide.

DR. LYMAN: I wish to thank Dr. Mitchell for calling attention in the way he has done to this exceedingly important subject. My own experience verifies all the doctor has said. I will not go over any recital of cases to prove it.

There are certain points which suggest themselves in this connection, and one is the question of heredity, whether there was any hereditary predisposition to insanity in the cases observed. Another question is how far the arthritic diathesis might have been responsible for some of these manifestations. We know that in cases of arthritic diathesis depression of spirits and great irritability of temper is one of the consequences. I infer from Dr. Mitchell's paper that at least one of his cases was one in which the arthritic disposition existed and might possibly have been responsible for the depression and irritability of temper.

The point made by Dr. Hare that potassium salts should be prescribed with care in chronic cases, is a very important one, for the potassium salts have a decidedly depressing effect upon the heart. In ordinary cases of melancholia, the alienists tell us that weakness of the heart is one of the prominent symptoms, and one of the causes that induces this melancholy depression. I have, in consequence of observation and also upon theoretical grounds, for many years discontinued the use of bromide of potassium in the treatment of epilepsy and kindred diseases, only occasionally using it in obdurate cases, my preference being for the sodium salt.

DR. W. H. THOMSON: I was called to a man who had suddenly become insane. I found him very talkative and rambling, and took it to be a case of acute mania. I discovered that he was taking large quantities of bromide for sleeplessness and nervousness. I had this stopped, and although the trouble had continued for ten days it ceased in two days, and the man recovered.

Two other cases that I wish to speak of were epileptics who had been under full treatment with the bromide—one by myself for long periods with free doses of the potassium salts. I first detected symptoms of bromine in one by his tottering gait, and ordered the bromide to be diminished. It was not diminished by the family from the fear that the fits would return, from which he had been free for some twelve months. He disappeared from the house suddenly and search had to be made for him. They were living at their country place on the Hudson, and five days afterward he was found some six miles distant, where he was paying a visit to people with whom he was but slightly acquainted. He told them that he had come to pass a few days. They could not guess the reason of his so favoring them with a visit, but did not, for some mysterious cause, notify his friends. He had taken his bromide with him. I ordered the discontinuance of the drug altogether, and he recovered in a few days, and never had a return of such symptoms. The

other was a serious case of epilepsy in a young lady, beginning early in life. One day while walking with her mother in the street she bowed to her mother and said "good-by, you will not see me again," and started to run. The mother called a policeman and the patient was brought home. She was quite maniacal. She tried to run away several times afterward in the course of a few days. The bromide was stopped altogether, and she recovered in the course of forty-eight hours after the bromides were discontinued.

I have no question that there are cases of mental derangement due to large doses of bromide, and that this fact should be taken into consideration.

DR. C. L. DANA: I must confess that I feel rather skeptical regarding the action of potassium salts upon the heart and nervous system as having anything particularly to do with the effect of the bromide of potassium. I have heard that statement made and have seen it published for a number of years, and have kept it in mind in prescribing the bromides, but I have never been able to see any particular difference between the amount of depression whether the patients were getting sodium or potassium salts. On the other hand, I have seen perfectly typical bromide depression produced by hydrobromic acid, and still further you know that potassium salts in the form of iodide of potassium are given in larger doses than we give the bromide, many patients taking 300 and 400 grains a day for a considerable period of time without any heart depression at all. I think that the potassium effect is a kind of "bugaboo" that it will be well to forget. Let us select our bromides on some other ground.

In regard to the pernicious mental effects of the bromide, I can agree with Dr. Mitchell, and I join with others in congratulating him upon presenting the matter with so much happiness and force. At the same time, I think there is another side which we at least should not forget. I have been giving bromides for a good many years, and I have never seen or known of a fatal case, with one exception. In that case the patient was treated by a homœopathic physician. With that exception I have never seen any serious results, and even these psychical disturbances, although alarming and to be watched for, are not often very serious. On the other hand, I think that Dr. Mitchell will admit that while bromides do cause depression and melancholia, and perhaps suicidal and homicidal state, at the same time if you give them in small doses they often have absolutely a cheering effect on many people. One trouble is that the physicians prescribe too large doses. The doses which I think will help and cheer are doses of 4 to 6 grains, and that is the ordinary dose in which I prescribe them.

DR. WHARTON SINKLER: It is a curious fact that the bromides which have such a marked influence for good on epileptic seizures, not only have no influence upon attacks of petit mal, but in large doses generally aggravate them. A couple of years ago a boy of ten years who was under my care was having one or two attacks of petit mal a week; previous to my seeing him he had been given bromides in fifteen-grain doses three times a day,

and had become profoundly under the influence of the drug. He was feeble, had drooping eyelids, and had a staggering gait. The attacks of petit mal had increased to from twenty-five to thirty a day. The attacks were at once reduced in number by stopping the bromide.

I have seen one death from the excessive use of bromide. The patient had been given bromides in excessive doses, and the autopsy showed absolutely no lesions.

DR. MITCHELL: I am surprised and interested at the additional matter that has been called out by my very modest paper, from which I expected very little. I thank the members for their additional contributions.

In regard to my friend Dr. Lyman's remark, that perhaps it would have been well to have obtained the previous family history of these patients, I beg leave to say that I was not engaged in any study of epilepsy, but only in the study of this one particular set of facts which I wanted to bring before the Association without needless detail.

Regarding Dr. Hare's remark, I may add to Dr. Dana's remarks that I never have been able to see any more depressant effects from the potassium salt than from any other of the bromic salts. I use principally the lithium salt when I use one bromide alone, because it contains the largest percentage of bromine of all the bromides, because it seems to be the best of them all for aiding in cases of insomnia, and perhaps because, being of all the most soluble, it passes readily into the blood.

I do think that some notice ought to be taken of this whole matter by those who teach therapeutics; they should warn their classes as to the use of bromides. I rarely go into a consultation in a case of apoplexy without finding the patient deluged with bromides. In most difficult or doubtful head disorders it is the primary resort of the general practitioner.

A CASE OF ŒSOPHAGEAL HEMORRHAGE WITH CIRRHOSIS OF THE LIVER.

By G. M. GARLAND, M.D.,
OF BOSTON.

It is not my purpose to treat of the various features of hemorrhage in cirrhosis, but simply to report a case of œsophageal hemorrhage that fell under my observation recently in consultation, together with two other cases; one of which was kindly sent to me by Professor Osler, of Baltimore, and the other by Professor Councilman, from the City Hospital in Boston.

This subject is extremely interesting, not only historically but clinically. The fact that up to some ten or twelve years ago this complication of cirrhosis was practically unknown, and men of such large opportunities, both clinically and pathologically, as Bamberger and Rokitansky, when their attention was called to the subject, testified that they had never seen such cases, or had only recognized one or two instances, lends to the subject great interest.

The condition was first discussed by a French writer and afterward was taken up by German writers, and in the last ten years cases have been gradually accumulating, which would seem to show that this complication is more frequent than at first sight would seem probable. This case which I report is the first one that I have ever met with. I saw it in consultation only a few days before the death of the patient. I, therefore, am using the notes that were made by the attending physician, who was also the patient's brother.

Case I.—J. D. S., American; married; produce dealer; height, 5 feet 9 inches; weight, 165 pounds; aged forty-nine years. Always well until the present attack. Saw him in November, 1888. He was then passing tarry stools. Said he had, during the past year, several such passages, and had also vomited dark-colored matter. Complained of feeling weak; no pain.

Ordered liquid diet and rest in bed. Made the diagnosis of probable ulcer of the stomach. Resumed business in about a week.

'On the afternoon of March 20, 1889, he was attacked with vomiting of blood. When I arrived, about an hour after the attack commenced, he was still vomiting. The vomiting occurred every five to fifteen minutes. His wife stated that that had been the case since the attack began. Under the sub. qs. of ergotin, grs. 5, the vomiting ceased in about an hour. The *vomicus* was in a large slop-jar; this I emptied into another receptacle for the purpose of inspection. It consisted of large, soft clots, slightly discolored, and some fluid-blood or gastric secretion, of perhaps a pint, but no food. It was my opinion, and also that of several present, that there were four quarts of coagula.

The patient vomited small amounts of blood on the 21st and 22d—perhaps a half pint each time—clotted and more discolored than at first. Sub. qs. of ergotin, grs. 3, were given once a day for a week. Diet, milk and lime-water. Tarry stools continued to be passed for about ten days. Convalesced in about six weeks. Slightly jaundiced.

Went to the country June 1, 1889, and remained until November 1st. Was again attacked with vomiting of blood at 7 P.M., November 26th; amount considerable, slightly discolored. Sub. qs. of ergotin, rest in bed, and rectal enemas. Two eggs, four ounces of milk, every six hours.

November 28th. Vomited a large amount, soft clots as before, slightly discolored. This vomiting was into a four-quart chamber, and it *more* than half-filled it. This vomiting was followed by an alarming collapse.

December 1st. Vomited between one and two pints of blood. Several days later, another small hemorrhage. Daily sub. qs. of ergotin, grs. 3, were continued. All food *per orem* was stopped, and rectal feeding relied on for alimentation. Two eggs, four ounces of milk, and six ounces of milk and one-half ounce of bovinine, alternately every six hours. The prostration very marked. Tarry stools with large quantities of very offensive *flatus* were passed continually until December 18, 1889, when he entered the Massachusetts General Hospital. For several days, however, before entering the hospital, the bowel had become so irritable that the food enemas would be retained only a short time, except the morning one following the cleansing enema.

Was discharged from the hospital February 4, 1890. Slightly jaundiced during his sojourn there, and for several weeks after. Gained flesh and strength. Said he felt well; and in October, 1890, entered the employ of the Boston and Maine Railroad as delivery clerk in the freight department. He continued work there, apparently enjoying perfect health until his attack in 1895; gained flesh until he weighed 200 pounds.

June 4, 1895, at 10 A.M., while at work, was attacked with vomiting of blood again. Walked home, a distance of about one-quarter of a mile, vomiting several times on the way. I saw him about 1 P.M.; was still vomiting. Gave sub. qs. ergotin, grs. 5, two injections, half an hour between. The vomiting

ceased at the end of half an hour. Emptied the vessel containing the *vomicus* into another. This contained what he had vomited after reaching his house. It was my opinion and that of the attendant that there were two quarts of blood and blood-clots, but little, if at all, discolored.

6th. Another attack. Vomited about a pint. Ordered absolute rest and rectal feeding. Two eggs, four ounces malted milk, two eggs and four ounces Mellin's food, alternately, every six hours. Sub. qs. of ergotin as before. Tarry stools with foul *flatus* from the first, and continued for about two weeks, then subsided, and stools became white and then clay-colored.

From the first of this attack I gave two drachms malted milk *per orem* every half hour to relieve the distress from the pangs of hunger from which he had suffered acutely in former attacks when only rectal feeding was allowed. This relieved all hunger, and he said he was perfectly comfortable.

About three weeks from the first attack he sat up. Went out in four weeks. Went to the beach July 4th, returned July 8th.

July 9th, at 10 P.M., was again attacked with vomiting of blood. Saw him at 7 A.M., July 10th. Did not see the *vomicus*. He and the attendant said the amount was large. A doctor had given him a sub. qs. of ergotin the night before. Rectal feeding, and two drachms malted milk by the mouth, as before. Tarry stools and offensive *flatus*, but no more vomiting, and he again entered the Massachusetts General Hospital July 12th. Discharged August 19th. Much emaciated and intensely jaundiced; passing clay-colored stools. Convalesced slowly; gained little, if any, flesh; gained strength somewhat more. Went to Biddeford Pool, Me. Seemed benefited by the change. Returned September 1st, still passing clay-colored stools. Jaundice still very marked.

September 15th. Went to Bradford Springs, N. H. Up to this time, since leaving the hospital, his diet consisted of malted milk, Mellin's food, soft-boiled eggs on toast, and thoroughly cooked oatmeal. His usual meal was two eggs on two slices of toast and a small saucer of oatmeal, with a cup of cocoa; the milk and Mellin's food being drank between meals, as he felt their need.

On leaving for the Springs I stated to him if the waters were of any benefit to him, the effect would probably be manifested in the improvement of the color of the dejections and of the skin. He visited me at the end of two weeks. There was a very marked improvement of the color of the skin, and I inspected the fecal discharge and found it colored all through with bile. He stated he drank freely of the water; that for the first four days its diuretic effect was pronounced; urinated every hour or two, both night and day. Amount of urine very large. Then the bowels took on a diarrhœal action. The second day after the bowels commenced to act freely, the stools became very yellow. The diarrhœa subsided after a few days. The stools remained yellow, and so continued until his last sickness.

He returned to the Springs and remained until October 16, 1895. Gained twelve pounds. Saw him on his return. Stools were still yellow and the jaundice had nearly disappeared. Returned to work November 1st.

November 15*th*. Was again attacked with vomiting of blood, perhaps a quart. Same treatment as at his last attack.

18*th*. Small amount of blood vomited. Jaundice returned. Tarry stools; loss of flesh marked.

23*d*. Vomited about a pint of blood, which was the last time he vomited any blood. Toward the last fluid-blood ran from his mouth, a spoonful or two at a time, on several occasions. The emaciation was so great at this time that I gave a tablespoonful of bovinine with the malted milk and Mellin's food every hour; no solids. Rectal feeding continued. On this he seemed to improve slightly. After two weeks he sat up and walked about his room. Stools still clay-colored.

December 12*th*. Another hemorrhage. Dr. George M. Garland then saw the case with me, and daily until his death. At this last hemorrhage the patient did not vomit. I had instructed him to restrain vomiting when he could do so, as the act would favor further bleeding, by the suction-pump action on the open bloodvessel. This restraint he continued up to the time of his death, although I believe there was constant hemorrhage from the fact that he had black or dark-colored fluid or semifluid discharges two to four times a day, and occasionally fluid-blood ran out of the mouth.

18*th*. At 12 M., had quite a severe chill. About 3 P.M., pulse 120, temperature 103½°. Complained of pain in the right hypochondrium. At 9 P.M. the temperature the same; pulse 110. Pain present, but not severe. At 9 A.M. on the 19th, pulse 100, temperature 102½°. Pain about as the night before. Tympanites marked. The pulse registered 100 to 110, temperature 102° to 103½° until death.

23*d*. Rectal feeding was discontinued, and the liquid food last mentioned continued every hour and a half. At no time was food ever rejected from the stomach. He was perfectly conscious up to this time, only complained of inability to remember. He did not again complain of pain. The bowels remained much distended.

From this time on he gradually lost consciousness, although would take nourishment when asked to, until the morning of December 26th. Died at 6 P.M. of that day. An autopsy December 27th.

The patient never complained of dyspepsia to my knowledge. Never, during the whole course of his disease, did he complain of pain until after the chill, although I frequently inquired for this symptom. He said occasionally he felt a slight burning and itching in the right side (indicating the region over the pylorus). For the last ten years, I should say from personal observation, he was a small eater. Never appeared to require much food to satisfy his appetite. When questioned in regard to it, said food tasted well and he had eaten all he wished.

Autopsy. Dr. W. H. Prescott makes the following report upon the above case: "Body well developed and nourished; rigor mortis present; heart not remarkable; lungs œdematous; spleen large and firm, weight 860 grams; kidney and pelvic organs not remarkable; appendix swollen, inflamed, and

gangrenous; slight amount of local peritonitis about appendix, which was bound down by fibrinous adhesions to iliac fascia; no fluid in peritoneum and no other peritonitis; intestines filled with tarry blood; stomach contained two quarts or more of fluid and clotted blood; plexus of œsophageal veins near cardiac end of stomach much dilated, and in one a hole large enough to admit a good-sized probe; liver small, surface of right lobe 'hob-nailed,' left lobe not so cirrhotic; microscopical examination showed much cirrhosis and some fat."

Anatomical diagnosis. Cirrhosis of liver; chronic passive congestion of spleen with chronic splenitis; acute gangrenous appendicitis, with local peritonitis; enlargement of the œsophageal veins with rupture and hemorrhage; œdema of lungs.

No other source of the hemorrhage was found.

This second case is kindly furnished me by Professor Osler, from the records of the Johns Hopkins Hospital, and is as follows:

CASE II.—J. G. S.; aged fifty years; admitted to the Hospital on July 5, 1890; discharged on the 23d of August. Readmitted March 26, 1891. Died July 30, 1891. On admission complained of dyspnœa, œdema of the legs, pain in the epigastrium. He passed a small quantity of urine. He had been perfectly well until 1886.

Joined the navy in 1860, and in 1886, while at Panama, had malaria. In 1887, typhoid. In 1888 he had fever associated with jaundice and slight œdema of the legs. His dyspnœa began three months before first admission, and in May, 1890, the œdema became more marked. He had been a moderate drinker and had lived well. On admission there was some lividity of the lips and hands; the pulse was rapid, occasionally intermitting. There was no jaundice; no heart murmurs. The veins at the base of the neck were distended. He left the hospital much improved, but in December the œdema returned and in January the dyspnœa also. On the 6th of April, following an attack of diarrhœa, blood was noticed in the stools. On the 23d the abdomen was tapped and 6000 c.c. of yellow serum drawn off. On the 1st of June, 6400 c.c. were again removed; on the 7th of July, 12,500 c.c. This time the edge of the liver, which was hard, was distinctly palpable. A hard, firm, irregular mass was felt to the left of the navel, reaching almost to the left costal margin. On the 23d of July the abdomen was opened, the peritoneal cavity drained, and washed with salt solution. The patient's condition following operation was, until 7.30 P.M., good; at this time he became delirious. There was hemorrhage from the bowel the next morning, consisting of fluid and clots, to be followed by two more at 11 A.M. and 3 P.M. Death occurred at 11.30 P.M.

Anatomical diagnosis. Dilated veins in suspensory ligament; atheroma of coronary arteries; congestion and œdema of lungs and hemorrhage into lungs; cirrhosis of liver; hemorrhage from erosion of dilated œsophageal veins. Operation wound in abdomen; fibrinous peritonitis; acute splenic

tumor; dilatation of œsophageal and lumbar veins; in the anterior abdominal wall there is an incision extending in the median line below the umbilicus for 7 cm.

Autopsy. Body of a large, strongly built, slightly emaciated man; no œdema except of the scrotum; the surface has a slight icteric color. The peritoneal cavity contains a large amount of clear and slightly yellowish serum. The peritoneum is covered generally by a thick fibrinous exudate and the small intestines are glued together by the same. There are old adhesions between the stomach, colon, omentum, spleen, and diaphragm; the veins in the round ligament are slightly enlarged. Both lungs are tightly adherent to the chest wall. The lower lobes are injected and contain numerous hemorrhagic patches.

The heart weighed 330 grams.

Endocardium somewhat stained with blood; in the papillary muscle a small amount of fibrous tissue.

The coronary arteries are dilated, thickened, and atheromatous.

The liver is tightly adherent to the diaphragm and the surrounding viscera, the veins in the suspensory ligament being dilated and tortuous.

The liver weighs 1200 grams. Surface was roughened by adhesions and by a fibrinous exudate. It is exceedingly irregular, large, round projections with shallow depressions between them occurring. The capsule is thickened and the portal vein measures 2 cm. in diameter. The gall-bladder is distended with bright-yellow bile. On section the liver is of a brownish color to which a yellowish tinge is added. It is firm and coarsely granular. The dimensions of the liver are 25 by 14 by 7 cm.

Tne spleen is somewhat enlarged, weighing 650 grams.

The kidneys together weigh 490 grams, and are somewhat swollen.

The stomach contains a large amount of fluid blood and coagula.

The œsophageal veins are much dilated and project into the lumen of the œsophagus; 15½ cm. from the stomach there is an erosion 3 mm. in diameter which passes directly into a superficial vein situated in the mucous membrane. On splitting up the mucous membrane numerous openings in the posterior wall, which pass directly into large venous spaces deeper down, are found.

The small intestine as well as the large contains fluid-blood.

From the peritoneum an organism was obtained which was regarded by Dr. Welch as the pneumococcus of Fränkel.

The next case occurred in the service of Dr. C. F. Withington, at the Boston City Hospital, February 17, 1896.

CASE III.—C. A. A., aged thirty-seven years, single. His father died of phthisis. In childhood had measles, chicken-pox, and scarlet fever. Well and healthy. Has masturbated since his boyhood; at present about three times a week. Has had gonorrhœa several times, and fifteen years ago had a chancre. Last had gonorrhœa six years ago. Has been troubled with

catarrh for years. Has had an occasional slight attack of rheumatism for three or four years. For several years feet have been swollen at times. No hemorrhoids or varicose veins. Six months ago noticed a feeling of distention after eating. There has been considerable gaseous eructation. No nausea or vomiting. Good deal of *flatus*. Bloating has grown more pronounced of late, particularly after supper. Three weeks ago noticed a little swelling in right epididymis. Drank quite hard until eight years ago. Smokes three cigars daily.

Two weeks ago there was so much pain and swelling in the right testicle that he went to bed, where he has been since. The abdominal distention has greatly increased since he has been in bed, but there has been much less *flatus*. Bloats up more after every meal, and there has been some pain across belly. Appetite is fair. His urine has been very thick and dark for several days. No swelling of feet for last two weeks. Of late has been rather short of breath. Never noticed yellowness of conjunctivæ until his attention was called to it to-day.

He was well developed and nourished; somewhat pale. The eyes were rather prominent; yellow sclerotics; pupils equal and regular, reacting equally to light and accommodation. Pulse regular, good strength and volume. Heart and lungs normal. Liver dulness from sixth rib to costal border; spleen negative; abdomen prominent, thirty-seven inches in circumference; tympanitic over a section of about five inches. Flat in flank; fluid wave. Œdema of the extremities. Reflexes normal; skin dry; papular eruption on back. External hemorrhoids. Genitals, old scar on foreskin. Some œdema of scrotum. Left epididymis somewhat enlarged. Right testicle about two inches in diameter, translucent. Right cord much enlarged.

On *February* 19*th* the abdomen was tapped, and about a gallon of clear, decidedly yellow fluid was withdrawn. Dr. Ogden reports on the fluid: "Color, straw yellow; sp. gr. 1013; reaction neutral; albumin $\frac{3}{4}$ per cent.; sugar absent; sediment, few round cells; rarely one slightly fatty, rarely a blood globule."

Liver felt distinctly after fluid was withdrawn two inches below costal border. Spleen is thought to be felt one inch below costal margin. Jaundice present.

Urine rather high in color; sp. gr. 1022; red; acid; albumin absent; diaz reaction negative; sugar absent; sediment, large deposit of urates.

Blood leucocytes at 2.15 P.M., 19,200.

23*d*. The patient complained a good deal of swelling and of weakness, particularly of hands. Scrotum was greatly enlarged. Abdomen rapidly filled, and on the morning of the 20th was as distended as before the operation. There was a cutaneous eruption on belly and legs, particularly on the calves. Patient slept very poorly.

On *March* 11*th* patient was tapped and six and one-half pints of clear yellow fluid withdrawn. On the 11th, the right leg was somewhat softer than at last note. Patient slept rather better for the last four nights, but required hyp-

notics. At 4 P.M. patient spit about half-pint of blood. Morphine sub. qs. given. On the 12th, at 5.40 A.M., had a large tarry stool, about half-pint; had another about 10 A M., about one pint. Pulse 172. Some delirium during the night and morning. Had another hemorrhage. Tarry stool from bowel at 8 P.M.; again at 10 P.M. Failed steadily from the morning, and died during the night at 2 A.M. Practically unconscious for last sixteen hours.

Autopsy was held by Professor Councilman March 13, 1896. The body length 159 cm. Well built. Abdomen distended; blood about nose, mouth, and face. Right leg and thigh considerably swollen. Heart weight 230 grams; valves and cavities normal. Lungs diffusely stained dark reddish-brown; here and there denser bluish-brown areas. In the branches of the pulmonary arteries are numbers of small emboli at the division of the larger branches. A few of the emboli were adherent. The spleen large, weight 370 grams. On section, pulp apparently not increased. Follicles distinct. Kidneys, combined weight, 295 grams. The capsule peeled off readily. On section, markings normal. The appendix 5 cm. long; bound down behind the cæcum by fibrinous adhesions. The liver weight 1560 grams. The surface fairly smooth. On section, lobules small, very sharply marked out, centres red, periphery yellowish white. The stomach much distended; contained about 400 c.c. of clotted blood. The intestines throughout whole extent contained brownish-black material, evidently due to blood. In the lower part of the œsophagus the longitudinal veins were all much distended and prominent. Three of these veins were ulcerated, and small thrombi were present in the vessels at the point of erosion. Pressure on these veins forced the blood into the œsophagus. There was more or less erosion of the surface of the œsophagus and in the immediate region of these eroded vessels. Above and below and in the stomach there were no signs of post-mortem change. The inferior vena cava was one-third filled by a large reddish-gray thrombus adherent to the posterior wall, which extended as high as the liver and down into the femoral artery and its branches. Beginning with the common iliac the vessels were completely occluded. The right inguinal glands were considerably swollen. The retro-peritoneal glands on the right side around the iliac vessels were much enlarged, softened, and on section a pus-like fluid-blood came from them. The retro-peritoneal fat tissue on the right side from the brim of the pelvis as high as kidney was also infiltrated with a yellowish, thin, purulent material. No lesions were found in the testes or epididymis. Half-way between the umbilicus and the pubes were three punctured wounds. No evidence of infection at this point could be discovered. Bladder and prostate normal.

Anatomical diagnosis. Cirrhosis of the liver. Dilatation of œsophageal plexus of veins, with rupture and extensive hemorrhage into stomach and intestines. Purulent infiltration of retro-peritoneal glands and fat tissue on right side above pelvis. Thrombosis of femoral iliac veins and inferior vena cava. Chronic splenitis. Emboli of lung. Hemorrhagic infarction of lung. Inhalation of blood into lungs.

Cultures. Spleen, numerous flat, transparent colonies with slight depression of centres; pure streptococci. Kidney, many similar colonies of streptococci; one colony of staphylococcus aureus; several of staphylococcus albus. Right lung, innumerable colonies of streptococci; many staphylococcus albus and aureus. Heart, a few colonies of streptococci. Liver, many streptococci; few staphylococci aureus and albus. Thrombi in inferior vena cava; many streptococci; one colony of staphylococcus albus. Cover-slips from pus around inferior vena cava contain great numbers of streptococci in long typical chains.

In commenting upon this report Professor Councilman says: "The case is interesting not only from the cirrhosis and the hemorrhage, but from the following streptococcus infection. I do not know the portal of entry of the streptococcus, but I suppose it was through the lungs, or the wound made by tapping. We very frequently have evidence of general infection after death, the infection being due to the entrance of organisms when the resistance of the fluids of the body is reduced to a minimum."

It is well understood now that the dilatation of the veins of the œsophagus is the result of an attempt of the overloaded portal circulation to empty itself around the liver by passing along the veins of the short curvature of the stomach, distending them and working up into the deep veins of the œsophagus. In explanation of some of these cases where the cirrhosis symptoms have been late in appearing in connection with the dilatation of the œsophageal veins, it has been assumed that such compensatory circulation has been sufficient to take off much of the pressure from the portal circulation, and thus diminish the distention of the abdominal veins and of the hemorrhoidal plexus.

It is useless to try to generalize from such a limited number of cases as regards diagnosis in conditions of this sort. There are one or two points, however, which have been impressed upon us. One is, that the hemorrhages may continue for a long time, and there may be intervals of apparent recovery. It seems a wonderful thing that the hemorrhages can continue for so long a time before the fatal ending, because in some of the cases the distention of the veins produces such pressure on the mucous membrane of the œsophagus that it atrophies away and leaves but a single layer of endothelial tissue between the blood and the lumen of the œsophagus. It would seem impossible that anything could be swallowed without rupturing this thin partition.

Another point is the regurgitation of the blood, or, rather, a welling up of the blood from the œsophagus. In the case I saw this was a marked symptom. In ulcer of the stomach and ulcer of the duodenum I do not recollect that this is a common symptom for the blood to well out of the œsophagus while the patient is lying quiet in bed.

There have been a certain number of cases reported where hemorrhage from the œsophageal veins occurred without cirrhosis of the liver; so hemorrhage from these veins is not an infallible symptom of cirrhosis. On the other hand, the above cases show that hemorrhage from the œsophageal veins may precede many of the other and more familiar symptoms of cirrhosis.

DISCUSSION.

DR. GRAHAM: A varicose condition of the veins of the œsophagus is not in all cases due to cirrhosis of the liver. In a case reported by Dr. McKenzie, of Toronto, to the Toronto Medical Society, fatal hemorrhage occurred in a patient seventeen years of age. The boy, who had previously been healthy, was a bricklayer's laborer, and had been accustomed to lift heavy weights. At the post-mortem examination a varicose condition of the veins of the œsophagus was found, as well as an opening from which the hemorrhage had taken place. The liver was quite healthy. Similar cases have been from time to time reported.

DR. WEIR MITCHELL: I saw a great many years ago a child who had scarlet fever very severely, and some months afterward began to have gastric hemorrhages for which we could not account. Finally, the child died from hemorrhage, and on post-mortem examination a very singular condition was found. At the lower end of the œsophagus, just above the opening into the stomach, were two or three dilatations of the veins, which the doctor who saw the case with me called œsophageal piles. The stomach had ten or fifteen such dilatations of the veins. There was no disease of the liver whatsoever, and nothing else to account for this singular malady. There was, of course, weakness of the thinned walls of the veins, so that on the slightest stress they gave way and deluged the stomach with blood. There was no other lesion that we could discover.

DR. JACOBI: As the hemorrhages in cirrhosis of the liver are mostly gastric or intestinal there must be a good reason why in these cases the hemorrhage was œsophageal. There must then be some local changes in the blood-

vessels. We have been told in the paper that there were dilatations, but the dilatation as such, unless it is very excessive, is no reason why a vein should burst. There must be a structural change, and it is to be regretted that remarks on structural changes are absent from the post-mortem report. There may be defects in the tissue of the walls of the veins as well as in the walls of the arteries, and pathological changes, though they be rare, such as atheromatous degeneration in the veins. In one, at least, of the patients reported by Dr. Garland there was advanced age, and atheromatous degeneration might well have taken place. I suggest that in future cases of the kind the structure of the bloodvessel walls be more thoroughly studied.

A CASE OF SUBPHRENIC ABSCESS.

By ELBRIDGE G. CUTLER, M.D.,
OF BOSTON, MASS.

SARAH A., domestic, aged thirty nine years, single, born in England, living in Boston, entered the Massachusetts General Hospital May 16, 1895. Family history good; no tuberculosis. Catamenia regular, painless. Past history: No acute illness; has always been well, but not vigorous; has had dyspnœa and palpitation on exertion for years.

Present trouble. Since arrival in America, eight months ago, her digestion has been decidedly out of order. At first had heaviness and distress after meals, sometimes immediately, sometimes two hours or more after; much belching and acid eructation. Vomited occasionally, large amounts as a rule; no blood. Kept at work, though not feeling up to it.

Seven weeks ago stomach gave out absolutely. Began to have severe pain directly after ingestion of food; frequent vomiting directly after food, with relief of distress. Much belching and acid eructation. Vomitus consisted of food undigested; never noted any blood or coffee-grounds.

For the last month has been much used up; severe pain in abdomen with fulness at night, which seems to push up heart and causes spells of dyspnœa and gasping for breath and palpitation. Legs swollen for last month if on feet much.

On the 13th (three days ago) noticed sudden sharp pain in the left side of upper abdomen in waist; felt very ill. Long breath, cough, or motion caused severe pain in left hypochondrium. Some cough since; sputum white, frothy; no blood. Some vomiting; no blood. Has felt chilly and hot by turns; no rigor. Pain has continued in side, cannot lie on left side. Since the 13th bowels loose, two or three times a day.

Examination. Face anæmic and thin, looks as if she had been suffering much pain; lips anæmic. Pupils equal, react. Tongue dry, yellowish-white coat.

Heart's apex in fifth interspace, normal line; over base a soft systolic murmur, not transmitted.

Lungs. Right chest moves much more than left. Breathes with care as if fearing pain. At left base behind, flatness on percussion with absent breathing, voice, and fremitus to angle of scapula from below. At lower border of this area a loud friction rub extending into axilla and down in side to the

tenth rib. Above area of flatness some moist râles. In front flatness from lower border of heart down to line connecting tenth ribs. In left hypochondrium and waist extreme tenderness on palpation. A firm resistant mass felt below border of ribs from eleventh to eighth rib, very tender, not affected by respiration. Dulness to light percussion and tenderness throughout left abdomen. Area of gastric tympany reduced. In right side a firm mass, not tender, half the size of the first, descending with respiration.

Abdomen extremely rigid, especially in left side.

Vaginal examination. Uterus retroverted, not enlarged, slight tenderness in posterior cul de sac, nothing felt.

Rectal examination. Tenderness above to left.

Blood. White corpuscles 25,600 per c.mm. Hæmoglobin 55 per cent.

The surgeon having examined patient decided to wait. No food was given by the mouth for twenty-four hours. Hot laudanum fomentations, an enema, and a number of small doses of calomel relieved the patient, and a comfortable night was passed.

17*th*. Pain much less to-day when quiet; tenderness still acute. Signs as before. Bowels freely opened. Urine, fifty ounces in twenty-four hours; very slight trace of albumin. Specific gravity 1025. No diazo.

20*th*. Pain present only with cough or movement; tenderness still acute in left hypochondrium, with flatness and firm resistance. Flatness in left back continues at same level, shifts somewhat with change of position. White corpuscles 17,600 per c.mm. Sweats excessively.

24*th*. To-day some pain at top of left chest in front. Friction plainly heard at left top and a few crackling râles; less tenderness in abdomen. No rub in lower axilla.

25*th*. Severe attack of pain over cardiac region to-day. A loud friction rub synchronous with heart-beats heard over whole pericardial area; no evidence of effusion. Abdomen less tender. Flatness continues. White corpuscles 16,200 per c.mm.

28*th*. Friction rub continued for two days over heart; now ceased; no pain; no signs of effusion; much cough; whitish sputum; no tubercle bacilli. Still râles and coarse rub in left top.

30*th*. Attack of sharp pain at base of right lung and axilla. Loud friction rub heard here. White corpuscles 13,500 per c.mm.

June 3*d*. Better. Temperature lower; no pain; no rub in left top or over heart or right base. Fluid still in left pleural sac at same level. No acute abdominal tenderness, still flatness one inch below costal border left, with a tender edge or mass felt with firm palpation. White corpuscles 17,700 per c.mm. Hæmoglobin 36 per cent. Urine thirty ounces in twenty-four hours, of the same character as before.

20*th*. Condition slowly improving; still zigzag temperature, rapid pulse, sweating, anæmia, leucocytosis constant, slight cough. Fluid in left back with flatness; vague resistance below diaphragm, less in extent, but shuts off stomach resonance on left.

29*th*. Pain, swelling, and tenderness in left neck above external jugular, apparently phlebitis; signs elsewhere as before. Sweats much. Body wasting. Bowels loose. White corpuscles 12,000 per c.mm. Friction rub left apex returned.

July 10*th*. Phlebitis neck all right. Much diarrhœa for five days. White corpuscles 9000 per c.mm. Temperature 99° Fahr. Seems as if she were discharging her pus by diarrhœa. Flatness in back continues, also flatness below ribs in front, though no edge of mass felt now save what appears to be the left lobe of the liver.

14*th*. To-day pain and friction rub left top. Vomiting. Much cough. Temperature up to 103° Fahr., evidently a new septic manifestation. Sweats much. White corpuscles 13,300 per c.mm.

16*th*. Signs to-day. Fluid in left back extending six inches up. Flatness below left costal border in front for one inch, reducing gastric resonance. Friction rub dull at left top. Swelling of neck over left external jugular, hard, not tender. Right kidney felt for two or three inches below ribs. Body wasted. Face anæmic. Sweats much. Leucocytosis, pyrexia, diarrhœa. Red corpuscles 3,908,000, whites 13,300 per c.mm. Urine 1021; slight trace of albumin. Indican increased. Bile present.

Transferred to east surgical side, Dr. F. B. Harrington. Etherized. Aspirated between the seventh and eighth ribs in back, and three pints serous fluid withdrawn. Cultures sterile. No change in flatness in front. Stomach inflated and found (Dr. Cutler) pushed to right, normal resonance to left zone.

25*th*. Less sweating. Breathing and cough easier. Temperature continues between 99° and 101° Fahr.

26*th*. Operation. Cut made in median line five inches long above umbilicus. Exploration shows left lobe of liver lower than normal, lying over normal stomach, resonance to left; liver normal, pancreas normal, spleen not felt. To left, stomach wall held to diaphragm posteriorly and laterally by adhesions. Finger breaks through into small cavity containing foul-odored inspissated pus. Opening made to this cavity in posterior axillary line below eighth rib, one inch of eighth rib resected and cavity curetted out. Packed with gauze and cavity allowed to wall off from peritoneum.

August 5*th*. Very comfortable, but slight temperatures. Aspirating needle entered to mass inside of walled-off cavity, nothing withdrawn. Phlebitis of left leg developed.

15*th*. Sits up daily, but still weak. Sinus still draining.

20*th*. Complains of tightness across chest, slight cough. Some dulness in left base of lung.

24*th*. Respiration rapid and labored; still phlebitis of left leg.

27*th*. Pleuritic effusion of right side to-day.

Sept. 1*st*. For last day or two much dyspnœa, and has failed steadily. Line of flatness in chest rising, and now is two inches above angle of scapula.

2*d*. Tapped under cocaine and forty-four ounces withdrawn by Dr. Harrington, with much relief; some shock followed, but patient rallied. About

four hours later sudden failure of pulse and respiration, became cyanotic, coughed up much blood-stained frothy fluid, and died in two hours.

Autopsy twelve hours after death. Rigor mortis present. Head not opened. Woman of small stature, very thin, lividity of dependent portions. In median line of abdomen, a few inches below sternum, a linear cicatrix four inches long perfectly united.

Chest. Right pleural cavity contained a quart of turbid serous fluid. Lung not retracted; on section considerable frothy fluid. Left pleura very much thickened, adherent at upper part; at lower part an encapsulated space containing serous fluid. Lung compressed, but without marked evidence of disease. Pericardium contained an excess of fluid.

Heart small, dark-brown color; microscopic examination showed considerable pigment in muscular fibres. Weight 190 grammes.

Peritoneal cavity contained one pint of milky serous fluid in lower part.

Stomach adherent to peritoneum, as was also the left lobe of the liver, forming a cavity above the stomach holding a small amount of fluid. Stomach small; mucous membrane found on section to be scarred by numerous white cicatricial depressions, in other places membrane thickened and near œsophagus projected as a polypoid mass.

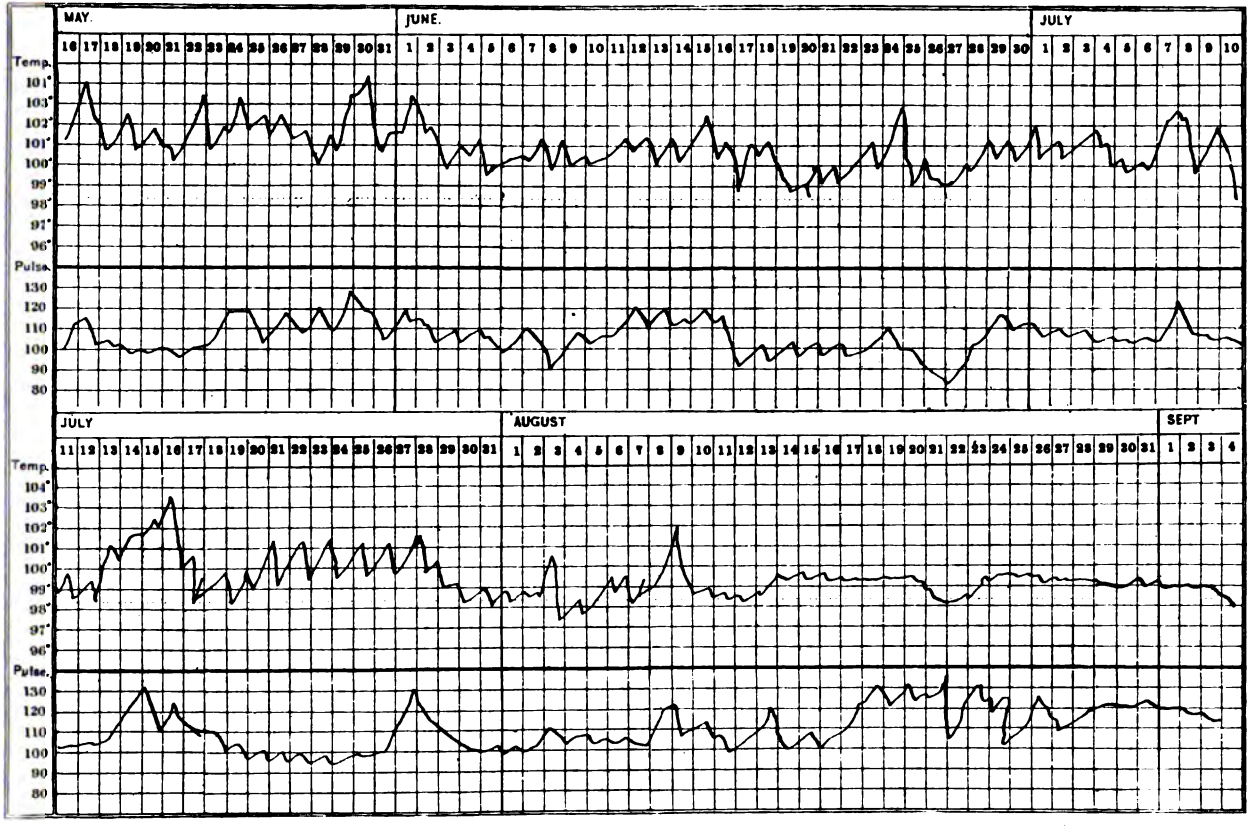
Intestines normal.

Spleen small, dark red, soft, weight 113 grammes.

Liver small, dark brown, weight 1215 grammes. Centre of lobules brown and yellow.

Kidneys small, markings distinct; microscopic examination shows them to be normal. Weight: right 115, left 113 grammes. Mesenteric and retroperitoneal glands very much enlarged, of opaque white color.

The diagnosis of subphrenic abscess, probably from perforated gastric ulcer, was made quite early in the case, but the surgeon declined to interfere till a change of service brought another on duty, and the operation was performed, but too late to be of much avail. The long duration of the case makes it at least probable that the patient would have had a better chance had she been operated on earlier.



Temperature and Pulse Chart—Sarah A.

ON ABSORPTION OF STRYCHNINE AND HYDROCYANIC ACID FROM THE MUCOUS MEMBRANE OF THE STOMACH.

An Experimental Study on Rabbits.

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The short account I intend to offer here of my experiments on the absorption in the stomach, I beg to consider only as a preliminary communication.

It has always been and still seems to be the prevailing opinion that the stomach is capable of absorbing soluble and diffusible substances, and there seemed, indeed, to be no reason for a supposition that the mucous membrane of the stomach should with regard to absorption be inferior to any other mucous membrane.

Recent investigations, however, have brought to light some new facts with regard to the power of absorption of the stomach, the most striking of which is surely the unexpected result that the stomach does not absorb any water. Edkins[1] had introduced into the stomach of cats after ligation of cardia and pylorus a measured quantity of saline, and recovered after an hour exactly the same quantity again. Von Mering,[2] who experimented on dogs with a duodenal fistula, found that a larger quantity of water came out through the fistula than the dogs had taken by the mouth. As my experiments will have reference mainly to the absorption of strychnine and hydrocyanic acid, I shall restrict my literary references only to those having any direct

[1] Edkins, J. S.: The Absorption of Water in the Alimentary Canal. Journal of Physiology, 1892, p. 460.

[2] Mering: Ueber die Function des Magens. Therapeutische Monatshefte, Mai, 1893.

bearing upon this subject. As far as I can ascertain there are only two statements on the absorption of strychnine in the stomach.

Bouley and Colin[1] have introduced strychnine into the stomach of animals whose pylorus was either ligated or paralyzed by vagotomy. They report that in the dog, swine, and cat the effect of the strychnine is very rapid; the effect was retarded in the cow; and there was no effect, at least no fatal effect, in the horse. Tappeiner[2] has experimented with strychnine exclusively upon cats, in whose stomach the poison was introduced through a stomach-tube. A normal cat of about two kilos succumbed to the effects of 0.03 strychnine in an aqueous solution in eight minutes; cats whose pylorus was tied succumbed to doses of 0.05 and more only after an hour and thirty minutes or even later. If the strychnine solution, however, contained some alcohol, the strychnine took effect almost as rapidly as when the pylorus was not tied. Tappeiner also found that chloral hydrate in aqueous solution was not absorbed in the stomach of a dog with closed pylorus, while an alcoholic solution of it was readily absorbed.

Of the effect of prussic acid upon the stomach I could find no reference.

My experiments extend over the absorption of various solutions in dogs and rabbits and also in frogs, but I shall report here only the results I obtained in rabbits with strychnine nitrate and hydrocyanic acid. The animals were all well narcotized with ether during the operation. In most cases, after the introduction of the poison into the stomach, the pyloric and cardiac ends of the stomach were tied. At the pylorus the ligature was applied in the groove between pylorus and duodenum, avoiding inclusion of the vessels of the stomach, and at the cardia the ligature was applied on the œsophagus just beneath the diaphragm. I shall now let the experiments speak for themselves.

Exp. 3. Rabbit, 1800 grams; not starved. Through a short catheter introduced by the mouth into the stomach 10 mgrs. of strychnine were injected, catheter removed and rabbit taken off from the board. After fourteen minutes a typical strong tetanus broke out; a few more followed, and the rabbit died.

Exp. 41. Rabbit, 1760 grams; not starved. Through an opening made in

[1] Colin: Traité de physiologie Comparée, vol. ii. p. 91.

[2] Tappeiner: Ueber Resorption im Magen. Zeitschrift für Biologie, 1880.

the œsophagus a catheter was introduced into the stomach and 6 mgrs. of strychnine in water colored with methylene-blue injected. Rabbit put in a box. After eighteen minutes, animal showed great uneasiness, and nine minutes later, with a sudden jerk, a strong opisthotonus set in, which lasted over two minutes. Rabbit remained hyperæsthetical for half an hour and gradually recovered.

These two control experiments are sufficient to show that 6–10 mgrs. of strychnine brought into the full stomach of a rabbit do not fail to produce within half an hour a characteristic effect.

Exp. 4. Rabbit, 980 grams; starved three days; stomach nearly empty. Cardia tied, an opening made in duodenum, and a thin catheter introduced into the stomach reaching the wall of the fundus. Sixty mgrs. of strychnine in 10 c.c. of a 40 per cent. alcoholic solution, colored with indigo carmine, were injected, the tube removed, duodenum and abdomen sewed up, and animal brought to the box. The rabbit lived fifteen hours, and at no time was there any sign of hyperæsthesia, increased reflex irritability, not to speak of a convulsion. The death was apparently due to peritonitis and "Schluck-pneumonie," but certainly not to strychnine-poisoning. The stomach was considerably distended and apparently contained more fluid than before the ligation.

The striking fact that 60 mgrs. of strychnine could remain for fifteen hours in the stomach without being absorbed could be attempted to explain by the claim that by the ligation of the cardia and pylorus, also all the bloodvessels and the lymphatics of the stomach were ligated, thus leaving no path open by which the poison could have been carried into the circulation. However, the stomach had by no means an ischæmic appearance; on the contrary, distinct pulsation could be seen after the ligation, and the stomach retained in every respect its natural appearance. At any rate, such a claim could not be raised against the following experiment:

Exp. 7. Middle-sized rabbit; pylorus ligated; cardia open; introduced through a catheter by the mouth 60 mgrs. strychnine in an aqueous solution. Rabbit lived nineteen hours without showing any effects of strychnine. Death and autopsy as in the preceding experiment.

Here the vessels of the cardiac end of the stomach remained open; nevertheless no absorption took place.

Exp. 28. Rabbit, 1200 grams; starved two days; cardia left open; introduced a tube through the duodenum into the stomach; injected into the fundus 45 mgrs. strychnine; rabbit remained for an hour on the holder, no

sign of any effect. Then the rectum was tied, and by a hypodermatic syringe injected through the wall of the rectum into the impacted lumen 3½ mgrs. strychnine colored with indigo carmine. After twelve minutes a tetanic outbreak set in, which terminated fatally. The tetanic outbreak was apparently due to the quick absorption of the 3½ mgrs. of strychnine from the rectum. No drop escaped into the peritoneal cavity or infiltrated the wall of the rectum, as could be seen by the absence of the blue color.

Against the conclusion that the mucous membrane of the stomach of the rabbit does not absorb strychnine, another objection could be raised, namely, that the stomach of the rabbit is never thoroughly empty and that the strychnine in all the cases is enveloped by the remnants of the food and does not come in contact with the mucous membrane at all. To meet this objection, the following experiment was made:

Exp. 35. Rabbit, 1200 grams; starved sixty hours; stomach quite empty. By a catheter, which was introduced through an opening in the œsophagus, 100 c.c. of water were brought into the stomach; catheter removed and cardia left open. A tube was introduced through duodenum and pylorus; the inner end of this tube was brought in close proximity with the wall of the stomach, when 60 mgrs. of strychnine, deeply colored with indigo carmine, were injected and some air blown in; now the tube was removed and the pylorus tied. An hour and twenty minutes passed by without a sign of a strychnine effect. Judging from the manifold experiences I had, I was sure that if the rabbit did not show the effects of the strychnine in the first hour the effect will not come any more. Therefore, the rabbit was used for another experiment. Three mgrs. of strychnine were injected through the anus into the rectum, which was not tied. After eight minutes a brisk tetanus carried the rabbit off. At the autopsy the stomach was taken out *in toto*. The entire stomach was transparent; the level of the fluid was distinctly visible; the level changed easily with each change in the position of the stomach. On opening the stomach, the contents flowed out easily, no food clung to the mucous membrane, and where the colored strychnine touched the mucous membrane there were distinct marks of the indigo carmine superficially adherent to the epithelial layer.

In this experiment the strychnine was surely in close contact with the mucous membrane of the stomach, and the vessels of the cardiac end were also not ligated; nevertheless, no absorption took place.

Exp. 40. Rabbit, 2100 grams; cardia tied; tube through duodenum into the pyloric part of the stomach; injected 50 mgrs. strychnine colored with indigo carmine, directed to the front wall of the pyloric part; this part bulged up; tube removed and pylorus tied. After two hours and five minutes still

no effect. Now 5 mgrs. of strychnine colored with methylene-blue were injected into the front wall of the stomach between the muscularis and the mucosa, a blue-stained area appeared, but no drop of the fluid escaped. After two minutes a stormy tetanus broke in like lightning and the rabbit was dead.

This shows strikingly that the ligation of the cardiac and the pyloric ends of the stomach does not prevent in the slightest the lymphatics and the bloodvessels from carrying into the circulation the fluid which gets at them.

In sharp contrast to our results with strychnine, we found that the stomach of the rabbit promptly absorbs prussic acid.

Exp. 6. Large rabbit; not starved; cardia tied; tube introduced through the duodenum into the stomach; injected 100 mgrs. of hydrocyanic acid (5 c.c. of the officinal 2 per cent. solution) colored with indigo carmine; tube removed and pylorus tied. Rabbit soon shows uneasiness, the breathing becomes labored, clonic convulsions set in, and the animal dies in fifteen minutes.

Exp. 26. Rabbit, 2200 grams; not starved; cardia ligated; tube through duodenum; injected into the fundus 60 mgrs. prussic acid; tube removed and pylorus tied. Rabbit dies after twelve minutes in the same manner as in the former experiment.

At the autopsies of some of the rabbits which died from prussic acid distinct hemorrhagic surfaces were found on the mucous membrane of the stomach. This probably accounts for the good absorption of the prussic acid; the fact that hydrocyanic acid was constantly absorbed from the ligated stomach of the unstarved animals shows that the acid easily reaches the mucous membrane even in a full stomach; and, further, that the ligation alone does not prevent the bloodvessels and the lymphatics from absorbing fluids which come within their reach. I have, therefore, in a few experiments with strychnine, used the absorption of hydrocyanic acid as a test for the points in question.

Exp. 12. Very large rabbit, 3200 grams; starved twenty-four hours; cardia tied; introduced tube through duodenum into the stomach and pylorus tied tightly around tube. At 5.12 P.M. injected 50 mgrs. strychnine in 10 c.c. water; at 8.28 rabbit perfectly quiet; injected again 50 mgrs. in 10 c.c. of 50 per cent. alcohol. At 9.28 rabbit sleeps well, no sign of strychnine effect. Injected now 100 mgrs. of prussic acid in an alcoholic solution; rabbit soon starts breathing irregularly, short inspirations, convulsive expirations, with

long intermissions; heart first slow, then very rapid, growing imperceptible: some clonic convulsions, no hyperæsthesia, no tetanic or tonic contractions; rabbit dies gradually within twenty minutes.

Exp. 42. Rabbit, 1740 grams; cardia tied; tube through duodenum into stomach; injected 200 mgrs. of strychnine in 20 c.c. of water; tube removed and pylorus tied. After one hour and fifty minutes no effect whatsoever. Sixty mgrs. of prussic acid, colored with methylene-blue, were now injected by means of a hypodermatic needle, thrust through the front wall of the stomach, directly into the mass of food; the fine opening clamped; nothing escaped. Very soon after the veins on the walls of the stomach show up a bright brick-red color; the same was seen on the edges of the spleen; irregular labored breathing set in; some clonic convulsions appeared without the presence of any hyperæsthesia; the rabbit died within twelve minutes.

The death was certainly due to the prussic acid, which rapidly reached the mucous membrane, penetrated it, and was carried off by the lymphatics and the bloodvessels into the circulation. The enormously large dose of strychnine has probably also reached the mucous membrane, and would also have been carried into the circulation if it could only penetrate the epithelial layer to reach the lymphatics and the bloodvessels.

I append two more experiments to show the character of absorption in some other parts of the alimentary canal.

Exp, 23. Large rabbit; cardia tied; tube through duodenum into the stomach; injected 40 mgrs. strychnine in a 33 per cent. alcoholic solution; tube removed and pylorus tied. After eight hours no effect. Then 14 mgrs. of strychnine were injected into the œsophagus, the upper end of which was tied. After one hour and thirty-five minutes still no effect. Now 4 mgrs. of strychnine were injected into the pharynx; in four minutes a brisk tetanus broke in, which brought a fatal end. Of course, it cannot be stated whether the absorption has taken place only within the pharynx or also in the mouth, and perhaps only in the mouth alone, though the injection was made directly into the pharynx.

Exp. 19. Middle-sized rabbit; œsophagus tied at the upper end and also below the diaphragm. The vagi and the inferior laryngeal nerves were avoided. Through a canula tied in the œsophagus, several injections were made in this tube. At first only 4 mgrs. of strychnine were injected, half an hour later 4 mgrs. more were added, and forty minutes after this again 10 mgrs. were injected. One hour and fifteen minutes passed after the last injection with no sign even of increased irritability. Now 4 mgrs. of strychnine were injected into a loop of the small intestine; after seven minutes there was already marked hyperæsthesia, and five minutes later a stormy tetanus gave death to the rabbit.

I have to add that in one experiment, half an hour after injection of 10 mgrs. of strychnine into the œsophagus, a tetanic attack did take place, but the œsophagus in this case was very much distended by air, which surely facilitates the absorption.

The results of my experiments, briefly summing them up, are as follows: Six to 10 mgrs. of strychnine brought even into the full stomach of a rabbit with pylorus open is sure to bring on a tetanus within a short time. The effect is probably brought about by the strychnine soon entering into the intestines, from whence it becomes absorbed in a few minutes.

When the pylorus, however, is closed, even such large doses as 200 mgrs. of strychnine, remaining for many hours within an empty stomach, with good circulation and with intact innervation of the vagi, do not produce any effect at all. *It seems that the mucous membrane of the stomach does not absorb even the smallest fraction of the strychnine.* Next to the stomach, we also found *that the mucous membrane of the œsophagus absorbs strychnine very poorly.*

The pharynx is apparently the part of the alimentary canal which absorbs best; 3 to 4 mgrs. in the pharynx will bring on a tetanus in three to four minutes.

The rectum absorbs nearly as well as the pharynx, as 3 mgrs. injected through the anus will call forth a tetanus in six to eight minutes. The absorption seems to take place here even better than in the small intestines, as it takes twelve to fifteen minutes before a tetanus breaks out after an injection of 4 to 5 mgrs. of strychnine into a loop of the small intestines.

Prussic acid is absorbed very well from the stomach even when the pylorus is ligated. It seems to produce a hemorrhagic surface on the mucous membrane which facilitates the absorption. Possibly, also, the prompt absorption of prussic acid is due to its volatility, as gases seem to be readily absorbed in the stomach.

DISCUSSION.

DR. A. JACOBI: The results of clinical observation may occasionally demonstrate the truth of what Dr. Meltzer has tried to find experimentally. There is no doubt, for instance, that morphine will show its effect much later when given internally than when allowed to be absorbed from the mouth. A few drops of Magendie's solution introduced into the mouth without any addition of water will have an effect within a very few minutes. Very obstinate coughing spells may not be relieved by any dose of morphine introduced into the stomach, but will be readily relieved by 4 to 6 drops of Magendie being taken in the mouth without the addition of water. I have utilized this experience during the last fifteen or twenty years, and I am satisfied that it is correct. This would correspond with the fact found by Dr. Meltzer, that the pharynx is a better absorbent than the stomach.

A STATISTICAL AND EXPERIMENTAL STUDY OF TERMINAL INFECTIONS.

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The part played by bacterial infection in the causation of death in chronic disease has gained in importance with the multiplication of observations upon the occurrence of such infections in human beings, the subjects of chronic heart, kidney, liver, and other disease. The data for a proper appreciation of the relation existing between bacterial infection and chronic disease are to be gained less by the clinical observation of cases than by systematic bacteriological examinations at human autopsies. The routine study of cases at autopsy by bacteriological methods will not infrequently reveal the presence of pathogenic micro-organisms which were, perhaps, unsuspected during the life of the patient. This fact has been demonstrated more than once in the course of the autopsy work at the Johns Hopkins Hospital, where for some time past it has been the practice to make routine bacteriological examinations. Indeed, such examinations have come to be regarded as belonging to the technique of the post-mortem examination. The data which the first part of this paper embodies are taken from the pathological records of the hospital, and represent the results of bacteriological examinations made by Drs. Welch, Councilman, Barker, Blumer, Livingood, and myself.

The routine examination of ordinary cases is readily made and does not take much time, while the investigation of general, multiple, and mixed infections requires much time and patience. The proper study of cases demands the preparation of cultures from the various cavities and all the viscera of the body, and this is equally true whether a

definite local infectious process is discovered or not. The distribution of bacteria is not always a regular one, and with a given local inflammatory process of bacterial origin secondary bacterial accumulations may be present in some organs and absent from others. Where no such special localization occurs only a complete set of cultures can be taken to exclude the possibility of bacterial development.

Negative results in bacteriological examinations do not necessarily afford positive proof of the absence of micro-organisms, as these may have been present in such small numbers as to escape detection, or have been irregularly distributed in an organ, or at the time of examination have been dead; or, finally, the culture media upon which they have been transplanted may not have been suitable to their growth. In view of some of these possibilities cover-slip preparations from organs and exudates should be made and examined along with the study of cultures.

Out of the 793 autopsies performed in the Johns Hopkins Hospital I have found in the records 255 in which occurred chronic heart or kidney disease, or both combined, and where the bacteriological examination was sufficiently complete to make them of use for this paper. This number does not represent all the cases of chronic heart and kidney disease that came to autopsy. In some the bacteriological examination was either not carried out at all or the records do not suffice for our purpose. Cases of tuberculosis are not included in this summary. Of the 255 cases mentioned 213 gave positive and 42 negative results.

If we direct our attention to the results of the study by bacteriological means of cases of chronic Bright's disease, in which the kidney lesions were the chief features, we find that of 32 cases, unassociated with heart or other chronic disease, 29 gave positive and 3 negative results. Similarly of 112 cases of combined chronic kidney and chronic heart disease, 85 yielded positive and 27 negative results. In a considerable number of cases of chronic Bright's disease other chronic diseases were present. These consisted of tumors, such as carcinomata, sarcomata, and myomata, of cirrhosis of the liver and lungs, chronic proliferative peritonitis, etc. Of 54 cases of combined chronic Bright's disease with one or the other of the diseases mentioned, bacteriological examination gave 51 positive and 3 negative results.

A similar study of the cases of chronic heart disease yields the following:

The number of cases of heart disease alone in which bacteriological examinations were made was 41, of which 32 were positive and 9 negative. The number of cases of chronic heart disease, associated with other chronic diseases than chronic Bright's disease, was 22, of which 16 gave positive and 6 negative results. The cases of combined chronic heart and kidney disease are the same as are given with the summary relating to the latter organ.

For the purpose of this paper no attempt was made to separate the primary heart from the primary kidney cases where both organs were affected. Again, the cardio-vascular system has been regarded as a whole, no division having been made into primary arterial and primary heart disease, given only that the heart was the seat of pathological changes. These consisted of hypertrophy with and without dilatation, disease of the coronary arteries, fibrous myocarditis, and chronic adhesive pericarditis.

The infections may be local or general. The former are much more common than the latter, and are found in a large proportion of all cases of chronic Bright's disease, arterio-sclerosis, cirrhosis of the liver, and other chronic diseases. Affections of the serous membranes (acute peritonitis, pleuritis, and pericarditis), meninges, and endocardium are the most frequent, but not the only lesions. Special localizations of the micro-organisms are met with in the viscera.

We shall first consider the general infections. No special group of bacteria is present in these in contradistinction to those present in the local infections. Not infrequently a local lesion, such as erysipelas, acute peritonitis, or acute endocarditis, exists which antedates the general invasion of the body by the infectious agent. It, however, may and actually does happen that the point of entrance of the micro-organisms cannot be made out at the autopsy. Either no lesion exists at the place of entrance or, as is more probable, it is so small and insignificant as to escape detection. Among the cases of general infection are found examples of cryptogenetic infection, in which the primary focus is so hidden that it is found at autopsy only after painstaking search.[1]

[1] Such a case was that of a young man who had a healed tuberculous lesion of the dorsal vertebræ associated with kyphosis. A general streptococcus infection, unsuspected during life,

In the series of chronic kidney disease are included 38 cases of general infection with the following distribution: Bright's disease alone, 3 (out of 29); combined Bright's and heart disease, 19 (out of 85); combined kidney and other chronic diseases, 16 (out of 51).

The micro-organisms causing these infections, 38 in all, were the streptococcus pyogenes, 16 cases; staphylococcus pyogenes aureus, 4 cases; micrococcus lanceolatus, 6 cases; gas bacillus 3 times alone and twice combined with the b. coli communis; the gonococcus, anthrax bacillus, bacillus proteus, the last combined with the b. coli, the bacillus coli alone, a peculiar capsulated bacillus, and an unidentified coccus each in one instance.

What is striking in this list is the preponderance of the usual pyogenic cocci. These may occur without being associated with abscess formation. In a large proportion of our cases of septicæmia visible focal lesions within the organs were not present at the autopsy. The usual conditions found were acute splenic tumor and more or less severe parenchymatous degeneration of the viscera, with sometimes microscopical necroses of tissue-cells as well.

No attempt has been made to separate the streptococci into distinct groups, and in this paper they are all included under the designation of streptococcus pyogenes, notwithstanding certain cultural differences noted in the behavior of specimens from different sources. For the most part the streptococci were not highly pathogenic for laboratory animals.

The character of the staphylococcus aureus is so well marked that no trouble is found with its classification.

The micrococcus lanceolatus was identified from its morphological and cultural properties, as well as its well-known pathogenic effects upon animals.

Concerning the bacillus aërogenes capsulatus it may be said that there is evidence of the distribution of the bacilli within the organ during life, although I am reluctant to admit a general invasion of the blood and tissues before death. The maintenance of life for any

was found at the autopsy. No source of the infection was present on the surface of the body, in the serous cavities or in the internal organs. Painstaking search revealed a small streptococcus abscess, imbedded in the deep muscles of the back, in the region of the healed tuberculous focus, which had developed at the site of that lesion. The heart of the individual was hypertrophied and dilated, the hypertrophy affecting chiefly the right side. The cavity of the thorax was small; the lungs the seat of chronic passive congestion. The myocardium was the seat of fatty degeneration.

length of time after this organism has established itself in the blood and produced gas there is probably impossible.

The cases of proteus septicæmia are of their kind unique and bear upon the growing belief that this group of bacteria may exhibit distinct pathogenic properties for man. The case of anthrax septicæmia is of interest as it was associated with an acute endocarditis and peritonitis due to the bacillus anthracis.[1] Of more than ordinary interest is the case of gonococcus septicæmia with localization upon the heart-valves.[2] A second instance of general infection with the gonococcus, following gonorrhœa, has just been noted by us. This case will be reported in full later by Drs. Thayer and Lazear.

In a few instances bacteria which could not be brought into harmony with any of the described pathogenic species were isolated, at one time from one or two organs, at another from a local inflammation, or, more rarely still, from several organs, or the heart's blood. These unidentified bacteria are reserved for a fuller description hereafter.

The portals of entry of the micro-organisms in these cases of general infection were in some instances made out and in others not. In some cases localized areas of inflammation existed which were taken to have antedated the general invasion. Not a few of these demand themselves an explanation of the point of entrance of the infectious agent.

Of the 16 instances of streptococcus infection the infection atria into the general circulation are believed to be as follows: Cellulitis, erysipelas, leg ulcer, bedsore, 7; phthisical cavity, 1; laparotomy, 2; tapping abdomen, 1; ac. pleurisy, peritonitis or pericarditis, 3; sloughing angio-sarcoma, 1; necroses of placental attachment in uterus, 1.

Of the 4 cases of staphylococcus aureus septicæmia they were: Acute pericarditis(?) following diphtheria, 1; operation upon the perineum and cervix uteri, 2; undetermined (gen. melanotic sarcoma) 1.

Of the 6 cases of micrococcus lanceolatus infection, acute pneumonia claims 4; acute endocarditis and acute pericarditis and pleuritis, 1 each.

The 5 gas bacillus cases give aneurism of the aorta opening externally, amputation of arm, each one case, and intestine 3 cases.

[1] Reported by Blumer and Young. Johns Hopkins Hospital Bulletin, 1895, Nos. 54–55.
[2] Reported by Thayer and Blumer. Ibid., 1896, No. 61.

The 2 proteus cases take their origin, 1 in a sloughing bedsore and the other from a chronic diphtheritic colitis.

The capsulated bacillus gained entrance from an ascending pyelonephritis; the anthrax bacillus from an anthrax œdema of the face.

The number of local infections is much larger. Of the cases of chronic Bright's disease alone 26 occur in which bacteria were present in some local situation; of the cases of combined kidney and heart disease 66, and of kidney and other chronic diseases 35.

The micro-organisms found in the local situations are, for the most part, the same as were met with among the general infections. They are not infrequently associated with one another, and occasionally it happens that the different organs contain different bacteria. Indeed, certain bacteria appear with such uniformity within certain organs that these must be regarded as presenting better opportunities for their growth than do others. Examples are afforded by the colon bacillus which is so commonly found in the kidneys and the lungs, and the occurrence of streptococci in congested and œdematous lungs.

The following table exhibits the variety, combinations, and frequency of occurrence of the micro-organisms found in the local affections:

	Times.
Streptococcus alone	14
Streptococcus and b. coli	15
Streptococcus and staphylococcus	2
Streptococcus and b. lactis aërogenes	1
Streptococcus and b. pyocyaneus	1
Streptococcus and unidentified bacilli	2
Staphylococcus aureus	8
Staphylococcus aureus and b. coli	3
Staphylococcus albus and b. coli	1
Streptococcus, staphylococcus aur., and b. coli	4
Streptococcus, staphylococcus aur., and b. lactis aërogenes	1
Micrococcus lanceolatus	12
Micrococcus lanceolatus and b. coli	3
Micrococcus lanceolatus, streptococcus, and staphylococcus	4
Micrococcus lanceolatus and streptococcus	1
Micrococcus lanceolatus and staphylococcus aureus	1
Micrococcus lanceolatus and b. aërogenes capsulatus	2
Bacillus coli communis	20
B. coli and b. diphtheriæ	1
B. coli, b. diphtheriæ and streptococcus	1
B. coli, streptoc., staphyl. alb., and unident. bac.	1

	Times
B. pyocyaneus and b. coli	2
B. pyocyaneus and b. lactis aërogenes	1
B. pyocyaneus, m. lanceolatus, and b. coli	1
B. pyocyaneus and streptococcus	1
B. proteus	1
B. proteus and b. coli	1
B. proteus and b. pyocyaneus	1
B. aërogenes capsulatus	1
B. aërogenes capsulatus, b. coli, and staphylococcus	1
B. aërogenes capsulatus, b. coli, and streptococcus	1
B. influenza	2
B. diphtheriæ	1
Staphylococcus cereus flavus	2
B. tetani, streptoc., s. aureus, b. coli	1
Gonococcus, staphyl. alb., and streptococcus	1
Undetermined bacilli	3

Upon analyzing this group we find that at least one place of localization is found in the following situations with the frequency mentioned:

	Cases.
Acute peritonitis	37
Acute pleuritis (without pneumonia)	11
Acute pericarditis	23
Acute endocarditis	19
Acute meningitis	4

In reference to this group, it may be said that along with the micro-organisms in the foci of inflammation the same bacteria as are present there may appear in one or more of the organs of the body. Their distribution is, however, not so general as to warrant their classification among the true septicæmias.

The varieties of bacteria which are present in these situations is shown by the following, which also exhibits the portals of entry of the micro-organisms so far as they could be determined with some probability:

Acute Peritonitis.

Bacteria.	Frequency.	Infection atrium.	
Streptococcus	8	Intestine	13 times.
Staphylococcus aureus and albus	9	Laparotomy	13 "
Micrococcus lanceolatus	4	Tapping abdomen	2 "
Bac. aërogenes capsulatus	2	Pneumonia	3 "
Bac. coli communis	3	Sloughing myoma uteri	2 "
Bac. pyocyaneus	1	Pyelo nephritis	1 time.
Bac. proteus	1		
Bac. anthracis	1		
Staphylococcus cereus flavus	1		
Streptococcus and staphyl. aureus	2		
Streptococcus and b. coli	1		
Streptococcus, staphyl. aur., and b. coli	1		
Streptococcus, staphyl., alb., and undeter. bacilli	1		
Bac. pyocyaneus and b. coli	1		
Unidentified bacilli	1		

Acute Pericarditis.

Bacteria.	Frequency.	Infection atrium.	
Micrococcus lanceolatus	11	Pneumonia	8 times.
Streptococcus	4	Bronchitis	2 "
Staphylococcus aureus	1	Erysipelas	1 time.
Bac. pyocyaneus	1	Leg ulcer	1 "
Bac. influenza	1	Tonsils	1 "
M. lanceolatus and b. coli	1	Peritoneum	1 "
Streptococcus, staphyl., aur., and b. coli	1	Cancer stomach	1 "
Staphylococcus and b. coli	2	Sloughing myoma	1 "
Unidentified bacilli	1	Doubtful	6 times.

Acute Endocarditis.

Bacteria.	Frequency.	Infection atrium.	
Micrococcus lanceolatus	5	Pneumonia	4 times.
Streptococcus	7	Intestine	1 time.
Staphylococcus aureus	2	Ulcer leg	1 "
Influenza bacilli	2	Sloughing carc. uterus	1 "
Streptococcus and staphylococcus	1	Abscess liver	1 "
Bac. pyocyaneus and b. coli	1	Carcinoma pylorus	1 "
Undetermined	1	Doubtful	10 times.

Acute Pleurisy.

Bacteria.	Frequency.	Infection atrium.	
Streptococcus	4	Peritoneum	4 times.
Micrococcus lanceolatus	2	Intestine	3 "
B. coli com.	1	Bronchitis	1 time.
B. proteus	1	Infarction lung	1 "
Streptococcus, staphyl. aur., b. coli	1	Doubtful	2 times.
Gas bacillus and b. coli	1		
B. coli and unidentif. bacillus	1		

Acute Meningitis.

Bacteria.	Frequency.	Infection atrium.	
Micrococcus lanceolatus	3	Ac. lobar pneumonia	3 times.

The intestine, as will appear from these statements, is regarded as the portal of entry not only of many of the bacteria found in the inflamed peritoneum, but also of some of those present in the pleura, upon the heart valves, and within the organs. This conclusion is based in part upon the behavior of those species which are known to be derived from the intestine, namely, the colon group of bacilli. It has been found that these bacteria wander through the intestinal walls with great regularity where lesions of the intestinal mucosa exist. The lesions present here need not for this purpose be considerable, as localized areas of hyperæmia and small hemorrhages often suffice to open the way for their escape; in grave lesions, such as necroses, ulcerations, and tumors, the colon bacilli are found almost without exception in some of the distant viscera. It is considered probable that the definitely pathogenic species of bacteria which are not infrequently associated with the colon bacilli in the intestine may find similar although probably not identical opportunities for escape.[1]

The occurrence of the colon bacilli in the organs is frequently unassociated with any lesions referable to their presence. Indeed, in the great majority of cases we have not looked upon the presence of a moderate number of colon bacilli as of pathological significance. In a few cases, however, they were present so generally in the body and in such large numbers that they could not be disregarded, and in rare instances they were found in association with definite lesions in such a manner as to leave no reasonable doubt of their pathogenic character. On the other hand, the frequent occurrence of the colon bacillus in combination with the pyogenic cocci is a matter of considerable importance, and, under such circumstances, these micro-organisms may come to have greater significance.

The majority of cases of acute pericarditis and acute endocarditis are found at the autopsy to be associated with pneumonia, either lobar or lobular in nature. As the micro-organisms present in the several lesions are usually the same, it is probable that the pneumonia is the source of the peri- and endocardial infection. Cases of pleurisy associated with pneumonia have not been included in our list. In some instances acute peri- and endocardial inflammations independent of pneumonia have been met with, and these may, indeed, be the sources

[1] See Flexner: "Peritonitis caused by the Invasion of the Micrococcus Lanceolatus from the Intestine." Johns Hopkins Hospital Bulletin, 1895, No. 49.

from which other serous surfaces become infected, or a general infection arises.

In cases of heart disease uncomplicated with kidney disease, terminal infections are encountered. Of 41 cases of arterio-sclerosis and chronic valvular disease, cultures showed in 32 the presence of bacterial infection, while in 22 cases of cardio-vascular disease, associated with some other chronic condition than Bright's disease, positive results were obtained in 16. In these 48 positive cases the distribution of the bacteria was general in 14 instances. The micro-organisms associated with these septicæmias were streptococcus pyogenes, 9 cases; micrococcus lanceolatus, 2 cases; staphylococcus pyogenes aureus, 1 case; staphylococcus alb. and streptococcus, 1 case; bacillus coli com., 1 case.

The portals of entry in the above cases are believed to have been as follows:

Streptococcus	Leg ulcer, ulcer scrotum, circumcision	3
	Laparotomy and peritonitis	1
	Abscess of back (kyphosis)	1
	Tonsil	1
	Carcinoma of stomach	1
	Sloughing carcinoma of neck	1
	Otitis media	1
	Doubtful	1
Staphylococcus aureus	Fracture of skull and acute meningitis.	
Micrococcus lanceolatus	Doubtful (no pneumonia).	
Bacillus coli communis	Intestine.	

The remaining 32 cases of infection were of local nature, and of this number 22 occurred in uncomplicated cardio-vascular disease, and 10 in combined chronic heart and other disease. As in the case of the kidney summary, we find here also that the variety of infecting bacteria is greater than in the cases of general infection. The following gives the kind of bacteria and the frequency and manner of their occurrence:

Bacillus coli communis	4
Streptococcus pyogenes	4
Micrococcus lanceolatus	4
Bacillus lactis aërogenes	1
Bacillus pyocyaneus	1
Staphylococcus pyogenes aureus	2
Staphylococcus pyogenes aureus and bacillus coli	1
Staphylococcus pyogenes aureus, streptococcus, gas bacillus, and bacillus coli	1

Streptococcus and gas bacillus	1
Streptococcus and bac. fœtidus	1
Bacillus coli and liq. bacillus (undetermined)	1
Undetermined bacilli	3

I would direct attention to the fact which must now be admitted, that the bacillus pyocyaneus which occurs several times in our tables, is, like the more common pyogenic organisms, capable of producing distinct and widespread lesions in human beings. We have met with several instances in which extensive necrosis, associated at times with ulceration, had been caused by it in the gastro-intestinal tract.

The special places of localization of the bacteria in the last series of cases is shown by the following summary:

Acute peritonitis	9
Acute pleuritis (without pneumonia)	6
Acute pericarditis	7
Acute endocarditis	15
Acute meningitis	3
	40

The micro-organisms which were isolated from each of the above situations were the following:

ACUTE PERITONITIS.

Bacteria.	Frequency.	Infection atrium.	
Streptococcus	5	Gastric ulcer	1 time.
Bacillus coli communis	3	Laparotomy	5 times.
Streptococcus and bac. fœtidus	1	Carcinoma stomach	1 time
		Circumcision	1 "
		Doubtful	1 "

ACUTE PERICARDITIS.

Bacteria.	Frequency.	Infection atrium.	
Micrococcus lanceolatus	5	Pneumonia	2 times.
Streptococcus	1	Tonsil	1 time.
Bacillus coli	1	Bronchitis	1 "
Gonococcus	1	Peritoneum	1 "
		Urethra	1 "
		Doubtful	1 "

ACUTE ENDOCARDITIS.

Bacteria.	Frequency.	Infection atrium.	
Micrococcus lanceolatus	7	Pneumonia	3 times.
Streptococcus	5	Pleurisy	1 time.
Gonococcus	1	Bronchitis	1 "
Streptococcus, staphylococcus aureus, and B. influenza	1	Tonsil	1 "
		Otitis media	1 "
Chain bacilli (unidentified)	1	Circumcision	1 "
		Urethra	1 "
		Acute endometritis	1 "
		Carc. uterus	1 "
		Doubtful	4 times.

ACUTE PLEURISY.

Bacteria.	Frequency.	Infection atrium.	
Streptococcus	8	Bronchitis	1 time.
Micrococcus lanceolatus	2	Circumcision	1 "
Gonococcus	1	Urethra	1 "
Negative	1	Doubtful	3 times.

ACUTE MENINGITIS.

Bacteria.	Frequency.	Infection atrium.	
Micrococcus lanceolatus	2	Pneumonia	1 time.
Streptococcus	1	Fracture of skull	1 "
		Operation on head, pharynx	1 "

This list leaves unmentioned a considerable number of cases in which, in the absence of micro-organisms in or inflammation of the serous cavities and upon the heart valves, pathogenic bacteria were found in one or several of the viscera. It would lead too far afield to consider the character of the lesions which may be associated with the invasion of the pathogenic bacteria which we have considered. But besides those which were at once evident to the naked eye, microscopic foci of cell degeneration and necrosis were frequently encountered.

The summary presented above will, if I mistake not, suffice to show the value of systematic bacteriological studies at human autopsies. It will also serve to impress upon you, as it has brought home to us, the importance of the *rôle* played by pre-existing chronic disease in determining susceptibility to infection, and to elucidate the statement recently made by a writer upon clinical medicine, namely: "It may seem paradoxical, but there is truth in the statement, that persons rarely die of the disease with which they suffer. Secondary infection, or, as we are apt to call them in hospital wards, terminal infections, carry off many of the incurable cases in the wards."[1]

Now that the subject of the intoxications is coming to have so much significance in human pathology, and there is reason to believe that many of the bacterial infections do harm by intoxication rather than by infection, *per se*, it might be pertinent to ask how far the operation of toxic substances may be responsible for still other examples of death in chronic disease, and whether there exists under these circumstances greater vulnerability to the actions of these poisons, just as we must admit a lessened resistance to the invasion of pathogenic bacteria.[2]

[1] Osler: Practice of Medicine, 1895, p. 132.

[2] Cf. Bouchard: Leçons sur les auto-intoxication dans les maladies. Paris, 1887. Roger: Action du foie sur les poisons. Paris Thèse, 1887; also, Rôle du foie dans les auto-intoxica-

The exact factors concerned in increasing susceptibility to infection in chronic disease are quite unknown. That the lessened resistance depends upon profound alterations in the body constituents is certainly probable, and in view of the disturbance of function associated with changes in organic structure, it is not difficult to form conjectures as to their possible character. We are also helped to a conclusion by the experiments upon animals, which tend to show that various injurious influences, by modifying the quantity and quality of the blood, the physiological nutrition and state of rest of the body as well as its normal metabolism, expose to infection.

It is exceedingly probable that pathogenic micro-organisms not infrequently gain entrance within the body in health, but do little harm there and are quickly removed or destroyed. We have abundant evidence of the power of the body to destroy many pathogenic bacteria which enter it from without or are introduced by experiment, and thus the conclusion that in chronic disease the mechanisms of disposal of bacteria are in abeyance or insufficient is not to be resisted.

The chief defences against the invasion of pathogenic micro-organisms are the body fluids and cells. To this activity of the juices of the body and certain of its constituent cells is doubtless owing our relative immunity from living disease germs. It is, therefore, of the first importance to know whether under the conditions which have been shown to predispose to infection there is a demonstrable difference in the bactericidal power possessed by these substances.

The experiments which will be given here have been made with the blood-serum of a number of cases of chronic disease from the medical wards of the Johns Hopkins Hospital. I wish to express my indebtedness to Dr. Osler for his courtesy in placing these patients at my disposal, and the house staff for their ready co-operation. For the purpose of comparison blood obtained in surgical operations from healthy individuals was employed. For the placental blood I am indebted to Dr. Dobbin, the resident obstetrician, who collected it for me in sterile tubes immediately after cutting the umbilical cord.

The blood of adults was obtained directly from veins by aspiration.[1]

tions. Gaz. des Hôpitaux, 1887, p. 65. Ewald u. Jacobson: Ueber ptomainactige Körper im Harn bei chronischen Krankheitsprocessen. Berl. klin. Wochenschrift, 1894, No. 2, p. 25. Albu: Ueber die Auto-intoxicationen der Intestinaltractus. Berlin, 1895.

[1] In two instances the blood was aspirated immediately after death from the heart and in another instance from the femoral vein. In all cases only sterile blood was employed, cultures upon agar-agar being employed for this determination.

A Roux syringe, sterilized by steam, was employed, the skin of the patient first having been scrupulously cleansed. This method is believed to have advantage over cupping as employed by Stern. Contaminations of the blood were never encountered, and 10 c.c. or even more were readily secured at a single operation. The blood was immediately transferred to Nuttall's bulbs, as it was found that the serum separated better in these than in test-tubes. After a period varying from two to thirty hours the serum was pipetted off into test-tubes, one cubic centimetre being the standard amount used in each experiment.

The bacteria which I have thus far tested upon human blood-serum are (1) staphylococcus pyogenes aureus, (2) bacillus typhosus, (3) bacillus of Friedländer. The experiments are most complete as regards the first-mentioned micro-organism, and the present report will refer exclusively to it. The reasons which led to the selection of the staphylococcus aureus for the first series of experiments are the following:

The study of the cases of terminal infections in human beings showed that the pyogenic cocci were the chief bacteria concerned with such infections. It was therefore considered most natural to expose these to the action of the serum. The staphylococcus aureus is not the chief invader in these infections; it is exceeded both by the streptococcus pyogenes and the micrococcus lanceolatus. However, the development upon culture media of the last two forms is subject to such variation under favorable conditions that the error of experiment must have been much greater than with the golden staphylococcus which presents no such difficulties.

Writers do not entirely agree as to the effects of the normal fluids of the body upon the pyogenic cocci, the majority (Nuttall,[1] Stern,[2] Prudden[3]) stating that they are quite without effect. On the other hand, Rovighi[4] considers that he has shown human blood-serum to possess bactericidal properties for the staphylococcus aureus. He also observed a reduction of this power for the staphylococcus aureus in two out of six persons suffering from severe cachexia.

[1] Zeitschrift für Hygiene, 1885, Band iv. p. 353.
[2] Zeitschrift für klin. Medicin, 1890, Band xviii. p. 46.
[3] Medical Record, 1890, vol. xxxvii. p. 85.
[4] Atti della Regia accademia medica di Roma, Anno 16, vol. 5, Serie 11, Rom. 1890.

In our experiments the blood of a number of persons has been subjected to study, and from the results obtained it will appear that normal human blood-serum *does* possess distinct bactericidal properties for staphylococcus aureus; and also that this power is absent, or, at least, diminished, in at least some cases of advanced chronic disease.

Our experiments show that the destructive effect exerted by the normal blood-serum upon the staphylococcus aureus is not an invariable quantity, and is at most much less marked than is observed with some other pathogenic bacteria, namely, the bacilli of Asiatic cholera and typhoid fever. It is, however, unjustifiable to compare, as has been done, the reduction in numbers which takes place when the golden staphylococcus is transplanted to blood-serum, with the diminution which regularly occurs after the introduction of the micro-organism into physiological salt solution. The two processes have little in common; the one, fluid (blood-serum), is at first destructive and after spending its power in this direction becomes a suitable culture medium, while the other (salt solution) permits at first a small increase of organisms from the nutriment carried over, and then leads in a relatively short time to a gradual, but often complete, disappearance from starvation of the added micro-organisms.

The method of determining the effect of the human serum was the one usually employed. It consisted of introducing a suspension of a young agar or potato culture of the staphylococcus aureus in physiological salt solution into the blood-serum. The same oese was used throughout each series of experiments, and care was exercised not to carry any of the nutritious material into the inoculated serum. Duplicate sets of plates were commonly employed. The inoculated blood-serum was kept at the temperature of 35.5° to 36° C. The agar-agar plates were permitted to develop at least for forty-eight hours at this temperature. For the enumeration of crowded plates the counter of Lafar[1] was used under a very low power (Ziess objective A_2, eye-piece No. 2) of the microscope. I also found this instrument very convenient for counting with the naked eye when a moderately large number of colonies had developed upon the plates. This method of estimation is not free from error; but when carefully conducted the duplicate counts are in remarkable accordance with each other.

[1] Zeitschrift für Nahrungsmittel-untersuchung, u. S. W., Wien., 1893, No. 24, p. 429. (Abst. Centralbl. f. Bakteriologie, 1894, Band xv. p. 331.)

NORMAL HUMAN SERUM UPON STAPHYLOCOCCUS AUREUS.

No.	Control plate.	1 hour.	2 hours.	4 hours.	6 hours.	24 hours.
1	33,764	.....	.....	4,823	11,255	Increase.
2	25,272	.....	18,925	8,424	4,212	Increase.
3[1]	10,920	7,800	7,210	5,740	.....	Increase.

PLACENTAL BLOOD-SERUM UPON STAPHYLOCOCCUS AUREUS.

No.	Control plate.	2 hours.	3 hours.	4 hours.	6 hours.	24 hours.
1	33,260	34,590	.....	39,912	.....	Increase.
2	73,632	67,494	.....	77,511	156,000	Increase.
3	46.566	.....	.....	56,000	200,000	Increase.
4	210 432	.....	.....	280,000	.....	Increase.

ABNORMAL HUMAN SERUM UPON STAPHYLOCOCCUS AUREUS.

No.	Control plate.	1 to 2 hours.	3 to 4 hours.	6 hours.	8 hours.	24 hours.
1[2]	33,764	.....	28,137	.....	4,220,500	Increase.
2[3]	57,720	52.000	.....	Increase.	.....	Increase.
3[4]	20 614	17,179	30,000	75,000	.....	Increase.
4[5]	11,154	13,013	.....	.....	50,193	Increase.
5[6]	50,000	.....	63,000	.....	.....	Increase.
6[7]	62,400	51,434	.....	100,000	.....	Increase.
7[8]	26,676	15,246	.....	10,166	6,356	Increase.
8[9]	66,456	32,000	.....	16,000	.....	Increase.
9[10]	14,742	9,828	952	.....	.....	Increase.

The foregoing tables show that of three specimens of average normal human blood-serum one only did not possess marked destructive power for the staphylococcus aureus, and with respect to this sample it may be questioned whether it is be to regarded as strictly belonging to this class. The greatest number of micro-organisms destroyed was 29,000 in four hours (Case I.), and 21,000 in six hours (Case II.). Of nine samples of blood taken from persons suffering with some form

[1] Blood from the enlarged veins in a myoma of the uterus.
[2] Arterio-sclerosis; mitral insufficiency; failure of compensation.
[3] Arterio-sclerosis; chronic nephritis.
[4] Arterio-sclerosis; multiple aneurism formation; chronic nephritis.
[5] Aortic insufficiency.
[6] Chronic nephritis; uræmia.
[7] Chronic nephritis; general anasarca.
[8] Arterio-sclerosis; aortic insufficiency. (Discharged improved.)
[9] Emphysema; heart hypertrophy. (Discharged improved after bloodletting.)
[10] Aortic and mitral insufficiency.

of chronic disease, in six no appreciable effect was exerted upon this micro-organism. Regarding the three in which more or less effect was produced, it is of interest to record those in two (Nos. 7 and 8), the patients improved while in the hospital, and the only one (No. 9) in which bactericidal effect was noted did the patient succumb to the disease within a short period of the examination. It is not a little surprising, in view of the other results given, to find that placental blood-serum exerts at most a temporary inhibition of development of this organism. On the other hand, the serum from these cases showed marked destructive power for the bacillus typhosus.

Taken together with the bacteriological studies at autopsies which have been presented, these results are considered to be of interest and to warrant still further investigation of the bactericidal power of human blood-serum under a variety of different conditions and upon a larger number of pathogenic bacteria.

Time does not permit a detailed consideration of the relation of immunity to the bactericidal property of the blood-serum, and, indeed, it is admitted that there is no fixed relation between these phenomena. Yet observations are not wanting to show that in both natural and acquired immunity a correspondence between this property of the blood-serum, or its absence, exists; however, not in all cases. The serum of the rat is destructive to anthrax bacilli, while that of man and the mouse have little or no effect upon these micro-organisms, and the serum of the rabbit varies in its behavior. Similarly the blood-serum of the immune guinea-pig, when diluted with bouillon, exerts injurious effects upon the cholera vibrio, which the normal serum fails to do.[1] The serum, too, of the vaccinated calf destroys the activity of the vaccine-virus, while the ordinary serum leaves it unaffected.[2] There is much significance, too, in the observation that just those micro-organisms, which are readily and quietly killed by the serum, are practically never found in the circulating blood in their respective diseases. Examples of this are furnished by Asiatic cholera and typhoid fever. Further, Flügge has pointed out that in anthrax infection in rabbits the bactericidal effect of the blood is lost before the bacilli make their way into the larger vessels.

Normal blood-serum contains, in addition to bactericidal principles,

[1] Pfeiffer: Deutsche med. Wochenschrift, February 13, 1896.
[2] Sternberg: Immunity and Serum Therapy, New York, 1895, p. 241.

antitoxic substances which must be of great importance in establishing and preserving immunity.[1] The comparative study of the antitoxic values of blood derived from persons suffering from chronic disease is reserved for a later communication.

DISCUSSION.

DR. STERNBERG: I was so unfortunate as not to hear the whole of Dr. Flexner's paper, but I heard one remark that I am particularly struck with, and that is in reference to blood which had passed through the placenta not having the bactericidal properties of the blood of the general circulation. This leads me to remark that it is an additional point in favor of a view which I have been disposed to entertain that the antitoxines when they are once in the circulation may, perhaps, be retained indefinitely, because they do not dialyze. One of the principal questions at present occupying the attention of investigators is as to the origin of the antitoxines. Is there a continuous production, or, having once been produced, do they remain for a length of time, or as long as immunity lasts? In some diseases immunity is of brief duration, as in diphtheria and cholera, and I think it is not at all improbable that if the antitoxines are developed during the attack a continuous development is not necessary, but that antitoxines remain in circulation for a considerable period simply because they cannot escape through the walls of the capillary bloodvessels.

DR. BOND: I would like to ask if an examination was made of the white corpuscles of the blood in these cases.

DR. THEOBALD SMITH: The problems of antitoxines and bactericidal actions are probably merely forerunners, so to speak, of more abstruse questions that will come up regarding the destruction of bacteria in the body. I have in my possession an organism at first sufficiently pathogenic to kill rabbits, but now attenuated. I used this in a series of experiments with the following results: By inoculating it in small quantities I produced a typical fever which lasted two weeks, after which there was a rapid recovery. After fifty days in one case and after a shorter time in other members of the series, I killed the rabbits and found the bacteria still in the liver, spleen, and kidney. They were present in small numbers, and it required comparatively large pieces of tissue, about the size of a split-pea, in order to produce the infection of culture tubes. I would ask why, after the animal had passed

[1] Escherich u. Klemensiewicz: Central. für Bakteriologie, 1893, Band 13, p. 153.
Abel: Deutsche med. Wochenschrift, 1894, Nos. 48 u. 50, p. 899 u 936.
Wassermann: Zeitschrift für Hygiene, 1895, Band 19, p. 408.
Fischl u. v. Wunschheim: Zeitschrift für Heilkunde, 1895, Band 16, p. 429.

through the disease, the bacteria were not entirely destroyed fifty days after recovery? Where were the bactericidal forces usually supposed to be aroused by the disease and to appear during and after recovery?

DR. BOLTON: It seems to me that the impression that Dr. Sternberg would leave is that the antitoxine never passes through the placenta. If that view is correct, I do not see how he could explain the results which Ehrlich and others have gotten, in which the mother has transferred the immunity substance to the offspring, not only in those cases where he injected abrin and such toxalbumins, but also in the case of tetanus where it is proved that the progeny of an immunized animal certainly contains a certain amount of antitoxine.

DR. STERNBERG: In regard to those cases of immunity in the young, I think they were shown to be due to the mother's milk. The young animals were not immune by reason of being born from an immune parent, but because of having taken the mother's milk.

DR. BOLTON: I would like to recall to Dr. Sternberg's mind that the experiments of Ehrlich were done by changing the young, taking the young of normal unimmunized mothers and giving that to a foster mother that was highly immunized, and *vice versa*. Although, as Dr. Sternberg says, the young from the normal mother derived a great deal of antitoxine through the milk of the immune foster mother, at the same time the young of the immune mother that suckled the normal mother had a large amount of antitoxine, and they could only have obtained this antitoxine while in the body of the mother.

DR. STERNBERG: I believe Dr. Bolton is right about that. For a moment that point escaped me.

DR. FLEXNER: I have made no study of the corpuscular elements of the blood in these cases. In reference to the point raised by Dr. Sternberg, I should like to say that the study of the placental blood was a mere incident in this work, and I was surprised to find an absence of the bactericidal property as described. I am not willing to apply this observation any further than it seems to hold for the staphylococcus aureus. The work of Fischl and V. Wunschheim, emanating from the laboratory of the pathological institute in Prague, upon the immunizing effect of placental blood obtained at childbirth, has shown that the placental blood in 85 per cent. of the cases contained definite antitoxic substances, and sufficed to cure diphtheria infection in guinea-pigs. The presence or absence of such antitoxic substances in the placental blood studied by me is not considered in this paper.

With reference to Dr. Smith's question, I agree with him that his observation is a most interesting one. I recall the report of an instance in which the typhoid bacillus was found by Welch and Blachstein in the bile of a rab-

bit one hundred and twenty-five days after the animal had been inoculated intravenously with the typhoid organism. The animal having survived the first injection was afterward inoculated with hog-cholera bacilli, and, succumbing to this, the bile still contained the typhoid bacilli. It can only be suggested that away from the fluids of the body, hidden in the recesses of the tissues, micro-organisms are not subject to the same conditions which exist in the circulating blood, and thus are not exposed to the same favorable opportunity for destruction. The experiment of Buchner, who enclosed anthrax bacilli in paper more or less permeable to the fluids of the body, and then introduced the packages under the skin of animals, shows that these bacilli which are killed by the extravascular blood-serum may live while surrounded, more or less, by the fluids of the body, but presumably less freely than in test-tube experiments. The injection of pathogenic micro-organisms, easily destroyed by the extravascular blood, into the blood-current for the purpose of testing the intravascular bactericidal effects, fails partly, at least, because the introduced organisms are quickly removed from the blood and deposited in the tissues (spleen, liver, bone-marrow), where they seem to be able to develop without such hinderance as the blood itself interposes.

SOME INVESTIGATIONS AS TO THE VIRULENCE OF THE DIPHTHERIA BACILLI OCCASIONALLY FOUND IN THE THROAT SECRETIONS IN CASES PRESENTING THE CLINICAL FEATURES OF SIMPLE ACUTE ANGINA.

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It is very difficult to dislodge from the minds of most practitioners of medicine the purely anatomical conception of diphtheria. Up to the period beginning with the discovery of the Klebs-Löffler bacillus and the development of the methods of bacteriological examination in the diagnosis of this disease, diphtheria was generally regarded as an inflammation of the respiratory mucous membrane, characterized by the formation of a false membrane, and this false membrane was considered to be the diagnostic feature of the disease.

Notwithstanding that previous clinical experience had shown that this was not a reliable criterion for the diagnosis of diphtheria, and notwithstanding that the evidence derived from thousands of bacteriological examinations in acute throat affections has demonstrated the fallacy of this view, there still remains the firm belief with a large proportion of the profession, that only such cases of acute angina are to be regarded as diphtheria as present at some time in their course more or less membrane. So thoroughly has this idea become fixed, and so strong is its influence upon practice, that many even of those physicians who unhesitatingly accept the Klebs-Löffler bacillus as the essential cause of diphtheria are still guided by it in their sanitary treatment of cases of true diphtheria, which simulate simple angina, and they do not regard the isolation and subsequent observation of such cases as either necessary or advisable.

Physicians readily enough acquiesce in the isolation of cases of

mild scarlatina or variola until complete desquamation has occurred, and no question arises as to the danger of transmission of such diseases to other persons through contact with mild forms, but similar reasoning is not allowed to apply to diphtheria.

The observations of Roux, Koplik, Park, and others, long ago proved that simple catarrhal angina, or what seemed to be clinically simple catarrhal angina, might be caused by the diphtheria bacillus. This fact was clearly brought out in an admirable paper by Koplik, published in 1892. Long before this time Trousseau, Jacobi, and other clinicians had shown that frequently during epidemics of diphtheria clinical anginas occur, which are as prostrating as those associated with the formation of membrane; and, in 1890, Roux directed attention to the fact that such cases, or very mild forms of angina without subsequent prostration, were not infrequently the origin of severe epidemics of diphtheria. The investigations of many observers, on the other hand, have proven that the presence of membrane does not necessarily indicate the existence of diphtheria, as membranous inflammations of the throat may be produced by other organisms than the diphtheria bacillus.

The purpose of the series of investigations detailed in this paper was to fix the exact value to be attached to the ordinary routine bacteriological examinations in determining the true character of the cases described. It was desired to ascertain in how large a proportion of the cases of simple acute angina the diphtheria bacilli would prove to be virulent in animal tests when they appeared to be typical in form and staining. Previous experience had led us to believe that the bacilli in such cases were almost invariably fully virulent.

The cultures selected for the observations were chosen from those received at the New York Health Department laboratories in which diphtheria bacilli were apparently found on microscopical examination, and in which the physician's diagnosis was doubtful or was tonsillitis. In some instances the diagnosis accompanying the cultures was simply tonsillitis, in others it was follicular, ulcerative, membranous or pseudo-diphtheritic tonsillitis, or pseudo-diphtheria, or acute pharyngitis, or diphtheria with an interrogation point. When cultures were received that had some such diagnosis as those referred to, and microscopical examination showed that they contained apparently typical diphtheria bacilli, the bacilli were plated out, pure cul-

tures obtained, and their virulence then tested upon guinea-pigs in the usual manner.

The bacilli derived from cultures made from forty-eight cases of this type were tested, and in only three instances were the organisms found to be non-virulent. In all of the remaining forty-five cases the animal tests showed them to be fully virulent. I may say in passing, that before the virulence of any culture was tested the character of the bacteria present in it was usually passed on by Dr. John S. Billings, Jr., and Mr. Alfred L. Beebe, who commonly make the routine examinations, and Dr. William H. Park and Dr. Anna L. Williams, who plated out the cultures and tested the bacilli for virulence. All these persons have had a very large experience in bacteriological work connected with diphtheria, and it will be readily understood that many cultures were thrown out as not showing typical Löffler bacilli, although they would be generally regarded as such. The subsequent history of the cases was obtained from the attending physicians by inspectors of the Health Department, and inquiry was made in each instance as to the source of infection and as to the occurrence of other cases in the family.

In four of the forty-eight cases the subsequent history could not be obtained. Of the remaining forty-four fourteen presented throughout their illness the clinical features of typical acute follicular tonsillitis, and in all of these the reports showed that the cases were of a mild character, and convalescence was fully established in from three to five days. In three instances the course of the disease was that of a simple acute pharyngitis of a mild type. In none of these seventeen cases was there any membrane in the throat at any time during the illness, and nothing in the clinical history suggested diphtheria. In a number of them the original cultures were sent by the physician in attendance, because one or more cases of diphtheria had already occurred in the family or in the institutions in which the patients were inmates, and in others the cultures were sent simply as a matter of routine, as is frequently done by many physicians in New York City. In one additional case the early history was that of a follicular tonsillitis, from which the child was apparently entirely convalescent, when suddenly croup developed with laryngeal stenosis, and intubation was required; in another the history was that of a follicular tonsillitis, excepting that after three or four days' illness the child became hoarse

and had a croupy cough. No antitoxine was administered, however, and the patient soon recovered. In the remaining twenty-five cases, while originally the diagnosis by the attending physician was follicular tonsillitis or was considered to be doubtful, ultimately membrane appeared, and the course of the disease finally was that of a more or less severe diphtheria.

Excluding the twenty-five cases in which ultimately the patients developed characteristic symptoms of diphtheria, there remain the nineteen cases which were clinically follicular tonsillitis or pharyngitis, with in two instances the development late of some laryngeal symptoms. In seventeen of these the tests upon animals showed that the bacilli found in the cultures were fully virulent.

In the analysis of this series of nineteen cases of apparently simple angina, associated with the presence of the Löffler bacillus as to the history of contagion, it was found that four occurred among the inmates of various institutions for children, in which diphtheria was at the time prevailing. In six of the remaining there was a history of previous or subsequent cases in the family, or the child was known to have been in contact with some person suffering from diphtheria. The history on this point in four cases was not given. It will be seen, therefore, that in ten out of fifteen in which the history was obtained there was reasonable evidence of contagion.

Examination was also made of the records in these nineteen cases to show the duration of persistence of the Löffler bacillus. This could be determined in fifteen of the series. The Löffler bacilli had disappeared in most of these cases within eight days of the time of the first culture. In one instance, however, they persisted for twelve days, in another for eighteen, and in another for thirty days. No subsequent tests for virulence were made during the persistence of the bacilli.

An important question arises in this connection as to the frequency with which true diphtheria simulates simple angina. There are no data at the command of the Health Department in New York which throw any light upon this phase of the subject. It has been found, however, that where virulent diphtheria bacilli are present in normal throats, as a rule, the history will disclose some recent exposure to diphtheria, and in a majority of the cases here described investigation proved that there was a definite source for the contagion.

From April 1st to the 28th notes were made of the clinical and

bacteriological diagnosis in every case from which cultures were received in the New York municipal laboratories. The number of cultures examined was much smaller during April than during some of the winter months. For this period, however, 2042 cultures were examined. Of these, 915 were primary, 944 were secondary, and 183 were trial cultures—that is, were made from the healthy throats of persons who had been in contact with diphtheria. Of the 915 primary cultures about one-half, 450, were made by the attending physicians. The clinical diagnoses accompanying the slips in these cultures were as follows: in 54 cases false diphtheria (usually tonsillitis); in 145 diphtheria or croup, and in 241 the diagnosis was doubtful or blank. The result of the bacteriological examination was as follows: false diphtheria 110, in contrast with 54 diagnosticated as such; true diphtheria 239, in contrast with 145 diagnosticated as such, and 241 in which the diagnosis was doubtful or blank. In 91 cases the bacteriological diagnosis was doubtful, either because the cultures were made too late in the disease, or were contaminated, or were unsatisfactory for some other reason. It therefore appears that out of 450 primary cultures received from physicians from April 1st to 28th inclusive, only 239, a little more than half, proved to be true diphtheria. During this same period there were reported to the Department, as diphtheria, 107 cases in which no cultures were made by the attending physicians, but those later made by the inspectors of the Department, on bacteriological examination showed no diphtheria bacilli, and the cases were therefore declared to be false diphtheria.

These data dispose of the statement which has been so constantly made and reiterated, that, as the result of the general adoption of bacteriological examinations for the diagnosis of diphtheria, the total number of cases of this disease have been largely increased by the addition of many cases of tonsillitis and pharyngitis which were previously regarded as simple anginas. As will be seen during the period referred to 107 cases considered as diphtheria, and reported as such to the Health Department, were excluded from the lists of reported cases of diphtheria by the bacteriological examination. During this same period only eighty cases considered by the physicians to be false diphtheria or of a doubtful nature were found on bacteriological examination to be true diphtheria.

There are no data at hand to show the exact proportion of cases

reported as follicular tonsillitis which on bacteriological examination prove to be true diphtheria. The proportion, however, is small.

A large number of cultures is sent to the Department in which no clinical diagnosis is given. Some of these prove to be cases of true diphtheria and some false. Whether they present the clinical features of diphtheria the Department has no means of ascertaining. Comparatively few physicians, however, send cultures from cases showing only the symptoms of follicular tonsillitis unless there are some reasons for suspecting the affection to be of a diphtheritic character.

The observations made on the cases detailed in this paper, while not very numerous, yet when taken in connection with those previously made in the Health Department laboratories, and the observations of Koplik and others, are sufficiently conclusive in showing that when diphtheria bacilli typical in appearance are found in cultures obtained from cases of simple angina (cases in which there is no membrane), animal tests, in a large majority of instances, prove that the bacilli are fully virulent. In other words, when morphologically typical diphtheria bacilli are found in cultures made after the rather rude methods employed in diagnostic work, the result of the examinations may be generally accepted as indicating the existence of virulent diphtheria bacilli, and the cases are to be regarded as cases of true diphtheria, unless animal tests have shown the organisms to be non-virulent.

We may refer, in conclusion, to the following classes of causes:

First. The healthy throats in which diphtheria bacilli are present. In these cases investigation almost always shows that the individuals have been in contact with cases of diphtheria. The presence of the bacilli in the throat without any lesions does not, of course, indicate the existence of the disease.

Second. The simple anginas in which virulent diphtheria bacilli are found. These are to be regarded, from a sanitary standpoint, in exactly the same way as cases of true diphtheria.

Third. Cases of true diphtheria presenting the ordinary clinical features of diphtheria and showing the Löffler bacilli.

Fourth. Cases of angina associated with the production of membrane in which no diphtheria bacilli are found. These might be regarded, from a clinical standpoint, as diphtheria, but bacteriological

examination shows that some other organism than the Löffler bacillus is the cause of the process.

It may be urged that the cases described in this paper were possibly instances of streptococcus inflammation of the throat in which diphtheria bacilli chanced to be present in the throat secretions, and were only accidental accompaniments and not the cause of the inflammation. This inference does not appear to be justified, and the only excuse for it would seem to be the desire to retain the anatomical conception of diphtheria, *i. e.*, that it is always an inflammation associated with the formation of a false membrane. It is this conception which I particularly wish to combat, and I desire especially to emphasize the statement that all inflammations of mucous membranes due wholly or in part to the Klebs-Löffler bacillus should be included under the name diphtheria without reference to the site or extent or intensity of the inflammatory process or the character of the exudate.

No.	Date.	Physician's diagnosis accompanying cultures.	Result of bacteriological examination.	Result of animal inoculation.	History of the case.	As to infection of others.	How contracted.	Remarks.
1	.....	Follicular tonsillitis.	Typical diphtheria bacilli.	Virulent.	Typical follicular tonsillitis; exudate disappeared in three days.	None.	.....	
2	 1896	Follicular tonsillitis.	Typical diphtheria bacilli.	"	Typical follicular tonsillitis; exudate disappeared in three days.	"	.....	
3	Jan. 7	Diphtheria?	Many suspicious bacilli; a few typical diphtheria bacilli	"	Clinically an acute pharyngitis; very mild.	2 cases: 1 mild; 1 very mild.	From brother.	No membrane present at any time.
4	" 9	Ulcerative tonsillitis.	Typical diphtheria bacilli.	"	Severe; septic; mixed infection; died.	?	.....	Antitoxine not administered.
5	" 9	Diphtheria?	Typical diphtheria bacilli.	"	Typical follicular tonsillitis, no membrane.	None.	....	
6	" 13	Membranous tonsillitis.	Typical diphtheria bacilli.	"	Mild; tonsillar membrane, disappearing after three days.	Diphtheria prevailing in the institution.		Inmate of charitable institution; removed to Diphtheria Hospital.
7	" 13	Membranous tonsillitis.	Typical diphtheria bacilli.	"	Mild; tonsillar membrane, disappearing after four days.	Diphtheria prevailing in the institution.		Inmate of charitable institution; removed to Diphtheria Hospital.
8	" 14	Diphtheria?	Many very suspicious bacilli; a few typical diphtheria bacilli.	"	Mild; tonsillar membrane, disappearing after three days.	Diphtheria prevailing in the institution.		Inmate of charitable institution; removed to Diphtheria Hospital.
9	" 16	Diphtheria?	Typical diphtheria bacilli.	"	A typical case of fairly severe true diphtheria.	None.	Not known.	
10	" 16	Tonsillitis.	Typical diphtheria bacilli.	"	Typical case of true diphtheria.	5 cases; the 4th case severe; the other cases mild.	....	Attending physician habitually marks slips accompanying cultures "tonsillitis."
11	" 18	Tonsillitis.	Typical diphtheria bacilli.	"	Mild, slightly ill; no other particulars could be obtained	None.	.....	Antitoxine administered twice.
12	" 19	Follicular tonsillitis.	Typical diphtheria bacilli.	"	Clinically follicular tonsillitis; very mild; not confined to bed.	"	Possibly from case in house.	
13	" 19	Pseudo-diphtheria.	Typical diphtheria bacilli.	"	Mild at first; later clinically true diphtheria with extensive membrane.	"	.....	Antitoxine administered
14	" 20	Follicular tonsillitis; possibly diphtheria.	Extremely small diphth.(?) bacilli.	"	Very mild tonsillitis; no false membrane at any time.	"	.....	Patient well isolated.
15	" 19	Tonsillitis.	Small, rather atypical bacilli.	Non-virulent.	Mild; "seemed to be tonsillitis clinically."	.....	.....	
16	" 22	Doubtful.	Large, pointed diphth.(?) bacilli.	Virulent.	Not obtained.	.....	.....	
17	" 22	Suspected diphtheria.	Very small typical diphtheria bacilli.	"	Severe.	Not known.	Not known.	

18	Jan.	23	Tonsillitis.	A few large, fairly typical bacilli.	Virulent.	A mild typical tonsillitis; not confined to bed; well in five days.	None.	Possibly from child in family.	
19	"	26	Follicular tonsillitis.	Small number of fairly typical bacilli.	"	Mild; course that of a true diphtheria; typical membrane.	"	.....	
20	"	27	Measles.	Typical diphtheria bacilli.	"	Severe; course that of a true diphtheria; paralysis of lower extremities.	"	From a case of membranous croup.	
21	"	27	Nasal diphtheria?	Typical diphtheria bacilli.	"	Mild; no constitutional symptoms; nasal diphtheria.	None; no other children in family.	.....	Antitoxine not administered; treated at dispensary during whole illness.
22	"	27	Diphtheria?	Typical diphtheria bacilli.	"	Mild at first, and diagnosis doubtful; became severe; course that of true diphtheria.	None.	.....	Adult; antitoxine administered.
23	"	27	Diphtheria?	Moderate number typical diphtheria bacilli.	"	Mild; course that of a typical acute tonsillitis.	"	.....	
24	"	28	?	Typical diphtheria bacilli.	"	Mild; course that of a typical tonsillitis.	"	.....	Antitoxine not administered.
25	"	28	Follicular tonsillitis.	A few fairly typical bacilli.	"	Very mild; clinically follicular tonsillitis; no membrane.	"	From aunt in same house.	
26	"	30	Diphtheria?	Typical diphtheria bacilli.	"	Mild; tonsillar diphtheria; membrane disappeared after two days.	Diphtheria prevailing in the institution.		Inmate of an institution; removed to Diphtheria Hospital; antitoxine administered.
27	"	30	Tonsillitis?	Typical diphtheria bacilli.	"	Moderate; no membrane.	Diphtheria prevailing in the institution.		Inmate of an institution; removed to Diphtheria Hospital; antitoxine administered.
28	"	29	Pseudo-diphtheria.	Typical diphtheria bacilli.	"	Clinically a case of true diphtheria; extensive membrane.	None.	From another case in same family three days previous.	
29	"	30	Membranous tonsillitis.	Typical diphtheria bacilli.	"	Moderate severity, tonsillar membrane disappearing after three days.	Diphtheria prevailing in the institution.		Inmate of an institution; removed to Diphtheria Hospital; antitoxine administered.
30	"	30	Follicular tonsillitis.	Abundant atypical diphtheria bacilli.	"	Mild; typical follicular tonsillitis; no false membrane at any time.	Diphtheria prevailing in the institution.		Inmate of an institution; removed to Diphtheria Hospital; antitoxine administered.
31	"	30	Follicular tonsillitis.	Typical diphtheria bacilli.	"	Mild; typical follicular tonsillitis at first; tonsillar membrane disappearing after three days.	Diphtheria prevailing in the institution.		Inmate of an institution; removed to Diphtheria Hospital; antitoxine administered.
32	Feb.	3	Follicular tonsillitis.	Typical diphtheria bacilli.	"	At first typical follicular tonsillitis, but membrane appeared (tonsillar) and persisted for five days.	Diphtheria prevailing in the institution.		Inmate of an institution; removed to Diphtheria Hospital; antitoxine administered.

No.	Date.	Physician's diagnosis accompanying cultures.	Result of bacteriological examination.	Result of animal inoculation.	History of the case.	As to infection of others.	How contracted.	Remarks.
	1896							
33	Feb. 6	Follicular tonsillitis.	Typical diphtheria bacilli.	Virulent.	Clinically true diphtheria; very severe.	None.	Not known.	Antitoxine not administered.
34	" 11	?	Typical diphtheria bacilli.	"	Mild; typical follicular tonsillitis; croupy and hoarse on third day.	"	" "	Antitoxine not administered.
35	" 11	Non-diphth. tonsillitis.	Typical diphtheria bacilli	"	Very mild, simple acute pharyngitis; no false membrane.	"	" "	Case recovered in three days.
36	" 12	Follicular tonsillitis.	A few bacilli, typical in shape; but with even staining.	"	Course of disease that of a true diphtheria.	.....	....	
37	" 18	Tonsillitis?	Typical diphtheria bacilli.	Non-virulent.	Clinically an acute tonsillitis, very mild.	Diphtheria prevailing in the institution.		Inmate of an institution.
38	" 18	Tonsillitis?	Typical diphtheria bacilli.	Virulent.	Clinically a case of true diphtheria, mild.	Diphtheria prevailing in the institution.		Inmate of an institution.
39	" 16	Diphtheria?	Typical diphtheria bacilli.	"	Began with convulsions and high fever; at first apparently follicular tonsillitis; later scarlet fever and diphtheria.	None.	None.	
40	" 27	Diphtheria?	Small, but typical diphtheria bacilli.	"	Clinically a very mild case of acute tonsillitis.	Diphtheria prevailing in the institution.		Inmate of an institution.
41	" 27	Diphtheria?	Typical diphtheria bacilli.	"	Not obtained.	Not known.	Not known.	
42	March 4	Pharyngeal diphtheria?	Typical diphtheria bacilli.	"	No information obtainable.	" "	" "	
43	" 6	Rhinitis and laryngitis.	Typical diphtheria bacilli.	"	No information obtainable.	" "	" "	Inmate of an institution.
44	" 8	Pseudo-diphtheria.	Typical diphtheria bacilli.	"	Clinically appeared to be a very mild acute pharyngitis; no membrane.	.....	From another case in family.	Except for occurrence of previous case no culture would have been taken.
45	" 11	Acute tonsillitis.	Typical diphtheria bacilli.	"	A moderately severe true diphtheria; extensive membrane.	.....	From another case (memb. croup) in same family, but in another house.	This and succeeding case in same family.
46	" 11	Acute tonsillitis.	A few typical diphtheria bacilli.	"	A moderately severe true diphtheria; extensive membrane.	.....	Same as above.	This and previous case in same family.
47	April 5	Follicular tonsillitis.	Typical diphtheria bacilli.	"	At first follicular tonsillitis, throat had cleared up; then severe croup requiring intubation.	Not known.	Not known.	Antitoxine administered, case recovered.
48	" 6	Follicular tonsillitis.	Typical diphtheria bacilli.	"	Appeared finally to be a moderately severe case of true diphtheria.	1 case, same family.	" "	

DISCUSSION.

DR. WELCH: It is, of course, a matter of considerable practical importance for the physician to know in about what proportion of cases in which he makes, on clinical grounds, the diagnosis of diphtheria he is likely to be mistaken. Our experience in Baltimore has been that of primary pseudo-membranous inflammations of the throat, diagnosed by the practitioner as diphtheria, over 90 per cent. prove to be genuine diphtheria by bacteriological examination. Dr. Biggs's paper appears to me to present the results of a thorough and valuable study, such as we have learned to expect from the laboratories of the Board of Health in New York.

DR. S. J. MELTZER: The main point brought out by Dr. Biggs, namely, that any case of angina follicularis which shows the presence of the Loeffler bacillus is to be considered as true diphtheria, can certainly be accepted without further discussion. The reverse of this statement, however, *i. e.*, cases where the bacillus is not found are not to be considered diphtheria, I would not like to accept without restriction. If in one or two cultures taken from some case of follicular tonsillitis the bacillus could not be found, this cannot be taken as a positive proof of its absence. In this connection I would like to remind you of the case reported by Dr. Kossel, of Koch's Institute for Infectious Diseases, where for two weeks the membranes of the throat were searched for Loeffler's bacillus, and none was found; nevertheless, the pus from the otitis media following the original angina contained the bacillus of diphtheria in abundance. The statistics of the Board of Health of New York City are based upon single cultures made by an inspector or an attending physician. If the bacillus is not found in the first culture, the case is treated as a non-diphtheritic one, which seems to me to be a very hasty conclusion. Now if even these statistics show the presence of the bacillus diphtheriæ in 65 per cent. of all the cases reported, we may rightly assume that the bacillus was present in probably 90 per cent of all the cases.

As to the diagnosis, I would say that Dr. Biggs is mistaken if he assumes that a diagnosis of tonsillitis means that the attending physician considers the case as not diphtheria. I can say for myself that I have often stated that I considered a case as being tonsillitis, and meant by it only an anatomical diagnosis, without reference to its being diphtheritic or not.

I wish further to emphasize that the presence of Loeffler's bacillus in the throat is by no means sufficient to establish a case of diphtheria, because there are a number of healthy people who harbor in their mouths and throats the Loeffler bacillus, just as we do not consider a person to have pneumonia simply because his sputum contains the diplococcus pneumoniæ. Two points are required for establishing diphtheria: a local lesion and the presence of Loeffler's bacillus.

DR. JACOBI: I would like to make a personal correction. Dr. Biggs quoted me in connection with the matter, and said that I stated that occasionally a simple angina was found to be diphtheritic. In those remote times, perhaps twenty-five to nearly forty years ago, even in my first paper on diphtheria, in the *American Medical Times*, of 1860 I was of the opinion, and expressed it, that during diphtheria epidemics almost every case of so-called simple angina, almost every case of so-called follicular tonsillitis, was a case of diphtheria. So the occurrence was not occasional, but frequent.

It has been a question with me whether the New York Board of Health was correct in claiming that every case in which there was a Klebs-Loeffler bacillus in the mouth, even in otherwise healthy persons, should be isolated and prevented from going about and attending to business. I am of the opinion that that is unnecessary. I believe that there are many here who have diphtheria bacilli in their mouths without ever having diphtheria or being in danger of developing it. A healthy mucous membrane is not infected with diphtheria though a bacillus is on its surface. I must say that I have frequently looked upon this practice of the Health Board as unnecessarily cruel.

DR. BIGGS: I would like to correct Dr. Meltzer. I did not say that where diphtheria bacilli were in the throat that would be considered diphtheria. I said quite the reverse of that: that, of course, the simple presence of diphtheria bacilli was not to be considered an indication of diphtheria. There must be an inflammatory process produced by them to constitute diphtheria.

The point that I wish to make particularly sharp is that diphtheria is an inflammatory process of the mucous membrane produced by the diphtheria bacillus; whether there be membrane present or not is immaterial.

The second point I wish to make is that when in the ordinary routine examination of throat secretions morphologically typical Klebs-Loeffler bacilli are found in the vast majority of cases, when tested on animals they are found to be fully virulent, whether the cases gave the clinical picture of follicular tonsillitis or of true diphtheria.

As to the absence of bacilli in some cases, or rather the failure to find them in cultures where they are present in the throat, this fact has been noted by all observers; but a culture properly made from the throat does show bacilli in the vast majority of cases if they are present there.

The experience which Dr. Welch referred to in Baltimore and Philadelphia has been our experience also; *e.g.*, in the large majority of cases in which there is a distinct pseudo-membrane the diphtheria bacilli will be found, except in those cases where it occurs in connection with some other infection, such as scarlet fever.

I think that Dr. Jacobi is wrong in regard to the frequency with which diphtheria bacilli are found in normal throats. We have made a large series of examinations of normal throats, and it has been the experience always that where diphtheria bacilli were found in normal throats that further in-

vestigation would usually show that those people had been in direct contact with cases of diphtheria. I do not believe that if cultures were made from the throats of all of the physicians in this room that diphtheria bacilli would be found in anyone. Such contact as ordinarily comes from attending a case of diphtheria by a physician does not usually lead to the presence of the bacilli in the throat. This is shown by the fact that we have made cultures from the throats of all the health department inspectors, who are constantly seeing cases in tenement-houses, half a dozen or more a day, and it has been the rarest experience to find in their throats the diphtheria bacilli. When diphtheria bacilli are found in healthy throats you may almost certainly say that the person has been in contact with a case of diphtheria, and usually in fairly close contact with it. This, it seems to me, is a very important point. There is misconception about the matter which has arisen from the discovery of diphtheria bacilli occasionally in the throats of healthy people and from the persistence of bacilli in throats after diphtheria. In a large series of examinations, even including cases in dispensaries, we found that only about 1 per cent. of the normal throats had diphtheria bacilli in them.

The question of the sanitary management of cases of diphtheria after convalescence, while the bacilli persist in the throat, what is to be done with such cases, this constitutes one of the most difficult problems in sanitary work and one which has not yet been solved.

PROGNOSIS IN PNEUMONIA.

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THE prognosis in pneumonia is modified by a number of pre-existing conditions, the principal of which are sex, age, season of the year, habit as to the use of alcohol, and the presence or absence of certain chronic diseases.

It is conceded that while pneumonia occurs more frequently in men, it is more fatal in women. Of 223 patients with pneumonia admitted into the Presbyterian Hospital, 170 were males, with a mortality of 28.8 per cent., and 53 females, with a mortality of 31.2 per cent.

Before the age of two years lobar pneumonia is a very rare disease. After that age the mortality is greater in proportion as the patient is older. In 16 cases under ten years of age at the Presbyterian Hospital there were no deaths; in the cases occurring in the second decade, 18.7 per cent. died; in the third decade, 19.6 per cent.; in the fourth, 28.3 per cent.; in the fifth, 39.4 per cent.; while of those fifty years of age and upward, 40.6 per cent. proved fatal.

The relative mortality of pneumonia in the different seasons of the year is variously stated by different writers. In the above 223 cases the spring months gave the lowest mortality, the summer showed a slight increase, while in the autumn and winter the death-rate attained its highest percentage.

The habitual abuse of alcohol unfits the system to bear up against pneumonia. Of eleven such cases, referred to by Ewing, as occurring at the Roosevelt Hospital, only three recovered. In the records of the Presbyterian Hospital the subjects of chronic alcoholism are not distinguished from those who habitually use alcohol though not to excess, the use of beer being included. With this wider definition

of the alcohol habit, the latter seems not to add materially to the mortality.

A pre-existing rheumatic habit has generally been observed to add to the gravity of the prognosis. It was present in twenty of the Presbyterian Hospital cases and was attended by a mortality of 40 per cent. As the rheumatic habit, however, is more pronounced as life advances, the influence of age in these cases must not be overlooked.

The prognosis is extremely unfavorable in diabetic patients. The combustion of the sugar, already imperfect, is diminished in proportion to the impairment of the respiration. Death in such cases is preceded by delirium and coma.

The pre-existence of chronic nephritis makes the prognosis of a pneumonia more grave in proportion to the renal insufficiency and the accompanying cardio-vascular changes.

Pneumonia occurring in a subject of advanced cardiac disease is likely to prove fatal. The prognosis is less grave before secondary changes have taken place in the right side of the heart.

Coming now to the conditions arising in the course of the disease, and which seem to influence the mortality, the first is the initial chill. This occurred in 144 out of the 223 cases, with a mortality of 34 per cent., while the remaining 79 cases in which the chill was absent gave a death-rate of only 19 per cent. From this it is evident that the chill is an expression of a severer grade of infection, and I have observed that usually a prolonged rigor with tardy reaction presages an unusual degree of muscular and nervous prostration.

As to the location of the lesion, the right lung is more frequently affected than the left, and also gives a higher mortality. Of ninety-four cases implicating the right lung alone, twenty-eight ended fatally, giving a mortality of 29.8 per cent., while only sixty-two cases involved the left lung alone, of which sixteen, or 24.5 per cent., were fatal. In thirty-nine cases both lungs were involved, with a mortality of nineteen, or 48.7 per cent.

A feeble pulse that is frequent in relation to the respiration and temperature has much the same prognostic significance as a heavy and prolonged chill. In my experience it indicates a profound specific infection, that is likely to carry off the patient at, or before, the crisis.

The respiration is always frequent in pneumonia, but when extreme frequency is associated with a high temperature, it has less significance than when it occurs without this association. In the former case it is due in part to the fever; in the latter it denotes extensive lung implication, and probably œdema, a perilous condition, but one which is often susceptible of being relieved.

Up to 105° the danger does not seem to increase materially with the rise of temperature. Thus in forty-five cases with the maximum temperature ranging between 100° and 103° the mortality was 26.6 per cent., while in ninety-nine cases with a temperature betweeen 103° and 105° the mortality was 26.3 per cent. The conditions that raise the temperature above 105°, however, immediately tell upon the death-rate. In forty-nine cases with a temperature between 105° and 106° the mortality was 32.1 per cent., and thirteen cases at 106° and upward gave 61.5 per cent. of deaths. Recovery, however, may take place though the temperature has attained an extraordinary height. Wagner has reported such a case in a boy five years old, the temperature having reached 109.2° F. Indeed, it is an error to attach too much importance to the temperature alone, so long as the condition otherwise remains favorable, the measures intended merely to control the pyrexia are indicated only in extreme cases. It cannot be too often repeated that to give coal-tar preparations according to indications furnished by the thermometer is to expose the patient to a real danger in an effort to relieve him from a fancied one.

There is a physical sign to which I called attention some years ago that I regard as important in the prognosis of pneumonia. I refer to the character of the valve-sound heard in the pulmonary area. The resistance in the pulmonary circulation which always exists in these cases must necessarily increase the tension in the pulmonary artery, provided the force of the ventricular systole is not impaired. With this increased tension come a sharper recoil of the blood against the valve-cusps and a greater intensity of the valve-sounds. It follows, other things being equal, that in this intensity we have practically a measure of the degree of obstruction to the blood-current in the lungs.

It is generally very easy to note as consolidation progresses the constantly increasing sharpness of the pulmonary second sound, and in favorable cases this accentuation, after reaching a certain point, is maintained with little change until commencing resolution renders

the circulation easier, when the valve-sound loses in intensity in proportion as the pulmonary condition improves.

But, unhappily, loss of accentuation of the pulmonary second sound does not always depend upon relief of the pulmonary circulation. It may signify, instead, a weakening of the right ventricle and a lessened power to force the blood into the artery. This comes when the right heart begins to flag either from exhaustion from excessive labor, or because of the depression arising from the specific infection. In either case, when we find the pulmonary second sound becoming weaker without any evidence of a favorable change in the condition of the lung, we may draw the conclusion that the right heart is failing and that the tendency of the case is toward a fatal termination.

The information furnished by the pulmonary valve-sound is much more reliable than that supplied by the radial pulse, for in most cases the chief peril is of failure or exhaustion of the *right* heart, and of this the condition of the radial pulse will give only indirect and inconclusive evidence. The right ventricle may be on the verge of exhaustion, while the left retains almost undiminished vigor, and the radial pulse then will simply indicate that less blood than usual is flowing beneath the finger.

Unfortunately it will sometimes happen that the region of the pulmonary area is occupied by noisy râles, so that it may be difficult or perhaps impossible to appreciate the action of the valve. But unless the dyspnœa is extreme the breath can be held for an instant, and for the practised ear the briefest moment is sufficient. An emphysematous condition of the left apex may also obscure the sound of the valve or render it inaudible.

As to the prognostic value of the data furnished in this way, I can only say that I have never seen disaster come in a case of pneumonia unless it was preceded by a period in which the pulmonary valve-sound was progressively losing in intensity. Or, to put it in other words, I have never seen a case with sharp and distinct pulmonary valve-sound in which a favorable prognosis as to the immediate future was not justified by the event. The weakness of the right heart that is indicated when the valve-sound becomes less intense takes place chiefly in two classes of cases. The first is that in which the system is overwhelmed by the virulence of the infection. These cases are marked by a severe and protracted initial chill, great muscular pros-

tration, a small and relatively frequent pulse, and marked involvement of the nervous system. We may well believe that in such cases the heart muscle is poisoned, and that consequently the right ventricle with the increased labor thrown upon it early becomes exhausted. Such cases are apt to prove fatal before defervescence takes place. If they can be carried beyond this period the prognosis is greatly bettered.

The second class of cases is made up of those in which from age, intemperance, previous illness, or other cause, the integrity of the circulatory apparatus is compromised in advance. Here we have a constant tendency to the invasion of fresh areas of lung, and to the supervention of œdema. This tendency, while it increases the labor required of the ventricle, is itself increased in proportion as the ventricle weakens under its burden.

In the medical literature of fifty or sixty years ago we find frequent reference to the "buffy coat" observed on the surface of blood drawn for the relief of inflammatory affections, and especially inflammation of the lungs, and it was held that the thickness of this coat was roughly in proportion to the severity of the inflammation. To-day we speak of leucocytosis as associated with many morbid conditions, and notably with pneumonia, and admit a certain relation between the number of leucocytes and the intensity of the process in which they have their origin.

The connecting link between the old conception and the new was furnished by the discovery of Virchow some forty years ago, that the buffy coat did not consist wholly of fibrin as before supposed, but that it included a mass of white blood-corpuscles afterward called leucocytes.

The exact relation between temperature and leucocytosis in pneumonia is not yet fully determined; but in general terms it may be stated that a high temperature in a vigorous subject carries with it a large number of leucocytes. From a prognostic point of view this is of great importance. Whether we consider the leucocytes as scavengers, and assume that they destroy the cocci which are the medium of infection, or whether we assign to the white cells a share in the production of antitoxin, certain it is that severe cases in which there is marked leucocytosis do better, as a rule, than similar cases in which the increase of white cells is relatively slight.

When the leucocytosis is inconsiderable it will generally be found that the system is not reacting energetically against the infection, a condition which suggests an unfavorable prognosis.

On the other hand, there may be a high degree of leucocytosis which is not due to the pneumonia pure and simple, but to some complication as pleuritis or pericarditis, and if this is not taken into account a faulty prognosis may result.

Ewing, in an excellent article in the *New York Medical Journal* of December 16, 1893, gives the count of the white cells in 101 cases, of which 37 were fatal. He says: "An examination of the deaths will show that in severe forms of lobar pneumania a slight leucocytosis is a very unfavorable sign. In 6 fatal cases the number of leucocytes was subnormal. In 11 fatal cases the average number was 9000. Not one case recovered in which the disease was even of moderate severity, when the number of leucocytes fell below 14,000. In several instances, again, a slight leucocytosis seemed at the time the only unfavorable prognostic sign in cases ending fatally."

M. Laehr, in an article on "Leucocytosis in Pneumonia," published in the *Berliner klinische Wochenschrift* in 1893, maintains that in pneumonia there is an unmistakable connection between the temperature and the leucocytosis. When the disease is at its acme the count of the white cells is at the highest, while at the crisis there is a falling off. In pseudo-crisis and in deferred resolution the leucocytosis continues though the temperature falls. In the generally constant agreement of the course of the fever, the amount of lung infiltration, and the leucocytosis, the author sees a dependence upon a fourth factor, viz., the intensity of the infection, that is, the quantity and quality of the bacillus poison and the power of reaction of the individual. He goes on to say: "Still more important is the prognostic significance. If the number of leucocytes does not fall with the decline of the fever we may conclude that the process has not yet arrived at a standstill. If it falls with the fall of the temperature, but rises again the following day, we must be prepared for a renewed attack of the fever or the occurrence of some form of complication."

R. C. Cabot (*Boston Medical and Surgical Journal*, August 3, 1895) gives the count of the white cells in forty-nine cases of pneumonia. Leucocytosis was present in forty-one cases with ten deaths; absent in five cases with five deaths; doubtful in three cases with two

deaths. He says: "As far as these figures go, therefore, it would seem that while the presence of leucocytosis is not a very hopeful sign, its absence makes the outlook bad. Moreover, in two of these five cases the other reasons for giving a bad or guarded prognosis were not present. The individuals were both under fifty, were not at all alcoholic or weakly, and there was nothing in the condition of pulse, temperature, nor the physical signs in the chest to lead one to expect a fatal result. Yet both went down with surprising rapidity, and without any reaction to vigorous stimulation and supportive treatment."

In a subsequent paper (*Ibid.*, March 22, 1894) he adds twenty-four new cases, without materially changing the conclusions to which his figures would point.

A remarkably high leucocytosis, especially if associated with a low temperature, suggests a suppurative complication. Thus in a case of pneumonia at the Presbyterian Hospital the temperature on the seventh day was 103° and the count 54,500. The crisis occurred the next day, but with a temperature of only 99° F. there was still a leucocytosis of 42,000. Examination showed that empyema was developing. In another case with a similar complication the count was 44,000, while the temperature was 101.3°. In eight uncomplicated cases the highest in eighty-one daily counts was 41,000.

At the Presbyterian Hospital, in cases in which we wish to follow the leucocytosis from day to day, we have adopted the plan of recording it on the temperature chart, allowing for each additional 3000 leucocytes a space on the chart equal to one degree of temperature. Regarding 9000 as the normal, this figure would correspond with the normal temperature line; 13,000 would be recorded on the 100-degree line; 16,000 on the 101-degree line; 19,000 on the next line above; and so on, the tracing being made in red ink. In this way the relation of the count to the temperature is apparent at a glance.

DISCUSSION.

DR. M. H. FUSSELL: I would like to know if Dr. Smith has made any observations on the effect of pregnancy on the death-rate in pneumonia? During the past winter we have had quite an epidemic of pneumonia in my part of the town, and I have had three pregnant women with the disease, all of them healthy, normal individuals, under thirty-five years of age, and all of them died. Whether this was a simple coincidence or not I do not know.

DR. MELTZER: I would like to know if any bacteriological examinations were made? Were the cases of pneumonia due to the diplococcus lanceolatus or to Friedlander's bacillus, or were there complications with streptococci? For instance, it is possible that such cases of pneumonia which are caused by the micrococcus lanceolatus will terminate more favorably with a temperature say of 105°, because the growth of this micrococcus is impaired by so high a temperature as 41° Centigrade.

DR. W. H. THOMSON: We have had three cases of pneumonia in pregnant women, and all three got better. Doctor Smith does not refer to one of the questions that comes up in prognosis, namely, the presence of herpes. It has been long regarded that a herpetic eruption is a favorable symptom. My own experience rather confirms this. One of the pregnant women who was very ill had a free eruption of herpes.

DR. HARE: During the past winter I have been interested in studying the relation of fever in regard to prognosis, and I hope that Doctor Welch will carry out Doctor Meltzer's suggestion and give us information in regard to the temperature that seems to be deleterious to these infecting organisms. I read a paper before the Pittsburg Academy of Medicine on this subject, and in preparing that paper I became convinced that in a large number of diseases, and particularly in pneumonia, fever was actually a protective process on the part of the body. Of course a fever which goes above 104° or 105° may cease to be beneficial, but moderate fever may be an effort of the system against the invasion of disease.

In those cases of pneumonia having an increased leucocytosis there is a more favorable prognosis, and if there is a considerable febrile movement we have a better right to think favorably of the ultimate outcome of the case than if we have pneumonia which involves either a small or large amount of the lung, but which is associated with comparatively little febrile movement. The disease in the virulent cases springs upon a man; the system does not seem to react to it, and as a result of lack of reaction leucocytosis does not come on, and the system does not carry out the processes which result in the manufacture of heat. I believe that in the manufacture of heat the processes developing the heat are useful in destroying the toxin in addition to

being deleterious to the micro-organisms themselves. Furthermore, the fever, in a certain proportion of cases, seems to aid distinctly in the development of leucocytosis. Further, in regard to what Dr. Smith says regarding the coal-tar products, I believe we have a sufficient amount of evidence to show that these do harm; that they to a certain extent inhibit leucocytosis; and that they diminish the production of heat. At one of the first meetings of this Association, Dr. Wood and Dr. Welch took part in a discussion on the use of these antipyretic drugs in fever, and one of the facts which was adduced at that time was that these so-called antipyretic drugs prevented the production of heat. On the other hand, cold bathing does not prevent the production of heat, but probably increases it, because careful studies have shown that the temperature of the interior of the body often rises temporarily under the cold bath. When the antipyretic drug is employed, oxidation processes are held in check, and the heat which is deleterious to the germ is not produced, whereas when the cold bathing is used the oxidation processes are actually increased and leucocytosis is increased, and the result is that this method of treatment aids the body in those processes which we think are protective, while the coal-tar products actually render the body less immune.

DR. WILLIAM H. WELCH: The evidence is in favor of the view that all cases of genuine acute lobar or croupous pneumonia are due to the micrococcus lanceolatus. It has been found that this organism does not grow at temperatures exceeding about 42.5° C. (108.5° F.), and that cultures at 41°–42° C. (105.8°–107.6° F.) rapidly lose their virulence.

Although there is some support from bacteriological studies in favor of the opinion that febrile elevations of temperature may exert some conservative or protective influence in enabling the body to resist infection, it cannot be said that the evidence is at all conclusive in favor of the theory that this influence consists chiefly in direct injury to the infective micro-organism by the heightened temperature. There are other conceivable ways in which fever may exert a beneficial action.

DR. A. H. SMITH: In regard to the bacteriological examination I think that question has been sufficiently answered by Professor Welch. I have had no opportunity of studying cases of pneumonia in pregnant women. With reference to herpes, I have nothing more than impressions. Herpes is not particularly noted in the statistics.

It seems to me that there is altogether too much stress laid upon temperature in these cases, and the simple effort to force down the temperature accomplishes nothing except to blind our eyes, especially if done by any chemical means. I believe that if it is done at all, it can be more safely done by means of the cold bath. On the other hand, if we have an hyperpyrexia and if the duration of the disease is not sufficiently great to bring about any cardiac degeneration, I think we should do better to let the question of temperature alone.

CASE OF WANDERING PHLEBITIS (PERIPHLEBITIC LYMPHANGITIS).

By WILLIAM P. NORTHRUP, M.D.,
OF NEW YORK.

THE purpose of this paper is to raise the question whether much of the so-called phlebitis complicating typhoid fever, influenza, and other infectious diseases may not be, in reality, periphlebitic lymphangitis. The following illustrative case is submitted in favor of the view that it may be:

The patient was a woman, aged seventy-two years, well-preserved, cheerful, energetic; one of whom it was said she was always "happy and interested in everything about her."

Her father and brother had frequent hemorrhages from the nose which seem to have been moderate; another brother and a sister died of hemorrhage of the lungs; the patient herself had from childhood been subject to frequent, profuse nose-bleedings and hemorrhage from piles. She had several miscarriages before the birth of her one living child, after which birth she suffered from milk leg. Apart from the above there was no significant family or personal history; no gout; no rheumatism. The patient herself had never suffered any serious illness.

One personal peculiarity of the patient was the conspicuousness of her veins in all parts of the body. From early adult life she had been unable to wear a low-neck dress because of this, and at the time of her illness, at the age of seventy-two, the veins were showing in her delicate skin in a way most rare; the dark-purplish color in contrast with the fair skin made one think of veins painted on a manikin by a rather clumsy amateur. This peculiarity is mentioned, not because it suggests anything in the etiological line, but because it by chance afforded an excellent opportunity for observing any changes in superficial veins.

The history of the present illness begins with ill-defined feelings of not being in usual good health for one or two weeks, during the last two days of which time she experienced pain in the region of her left hip. It was afterward recalled that the patient, contrary to her habit or temperament, was very much depressed in spirits. To improve her general condition, her

daughter took her to drive, and sought to entertain her by a visit to a loan art exhibition. While there the patient, to use her daughter's words, "seemed to give out altogether" and wished to go away. Thinking a little drive would do the patient good they turned into the park. Presently the patient became "dazed," stupid, could not see, talked incoherently, became ghastly pale, could not answer questions, and appeared to be dying. The daughter hurried the patient home and to bed. While undressing it was observed that the whole left leg was swollen and the left thigh looked bruised. Very soon after this I examined the patient, finding the left limb considerably swollen; color normal; warm; pitting a little on pressure, with something to attract attention to the left groin. There was diffuse bogginess over the whole region; on pressure in Scarpa's space an irregular, slightly nodular induration and moderate deep tenderness. The tenderness was not so severe as to preclude a thorough examination, but the bogginess rendered it difficult to determine definitely the condition of the underlying parts. The point which gave rise to the most anxiety of all in the exanmination was the fact that no pulsation could be felt in the femoral artery. On the other side it could be distinctly and easily felt, and subsequent examinations proved there was no abnormality in the collocation of parts on the affected side.

The case stood for the time then as follows: Sudden prostration; absence of femoral pulsation in left Scarpa's space; swollen limb; color of limb normal; temperature not sensibly different from that of its fellow. Body temperature 103° F.; stupor alternating with moderate delirium.

At this point in the history Dr. H. F. Walker saw the patient in consultation. His diagnosis was "lymphadenitis" and consequent diffuse œdema. The swelling in a confined space and œdema about, caused the artery pulsations to become imperceptible. This diagnosis seemed at that moment to explain all the symptoms. Dr. Walker had seen similar cases.

On the following day about six inches of the internal saphenous vein became hard, whip-cord feeling; very sensitive; finger-wide redness gradually developing along its course, and later a wide irregular œdema, the whole linear area being exquisitely sensitive. After lasting four days the œdema began to subside, then the redness. The vein could be easily seen and appeared to the sight to be normal. The whip-cord feel, however, still remained and the parts continued too sensitive to be handled. At this point it was noted that the œdema of the leg had not increased—had perhaps grown rather less. The patient gradually became more comfortable, the fever subsided, and general improvement was marked.

About a week from the first observation, and when the whip-cord was the only remaining evidence of inflammation about the saphenous, the outer aspect of the thigh, upper half, became tender, diffusely red, with wide area having a brawny feel. It became apparent that this advance had taken in a loop of communicating veins which were whip-cord-like and with a surrounding condition similar to that of the internal saphenous. The invasion of this new and extensive region was attended with constitutional symptoms,

chilliness, elevation of temperature (101° F.), rapid pulse (125), pallor, sighing, restlessness, marked irritability, and depression of spirits, with petulance and weeping, stupor, mild delirium. The constitutional disturbance lasted one to two days; the redness began to disappear on the fourth day, œdema was gone at the end of eight days, the whip-cord and tenderness alone remaining.

At this time it was interesting to speculate whether the lesion was in the vein wall, a thrombo phlebitis; if it should prove to be such, being a plainly visible vein, it would be interesting to observe what further use the patient would have of the affected veins, aggregating now about eighteen inches in length.

After a few days of rest there was another event of interest, another pain, chill (chilly sensations), moderate rise of temperature, whip-cord condition of another six inches of vein, finger-wide redness, bordering œdema, exquisite sensitiveness, this time reappearing about the internal saphenous vein, continuous with that of the first attacked. Now it was observed that all signs about the early affected veins had disappeared; there was, furthermore, an intimation that the lesion was not of the intima with thrombosis, but that the lesion was extravenous.

The walls of the veins were apparently entirely normal; blood could be easily stripped out of them, the current creeping back in plain view.

In this manner the cyclic process continued: intervals of repose of from three to seven days; measuring off six-inch lengths upon the vein; characteristic manifestations of chill, febrile reaction, whip-cord feel, finger-wide redness, œdema, sensitiveness, subsidence of all symptoms, complete return of the vein to normal.

The process followed the line of the internal saphenous vein to the lower third of the leg and there ceased. Hope was entertained in the household that "it would pass off at the toes," as suggested by the patient.

After the lapse of ten days to two weeks another chill with febrile reaction visited the patient, no visible vein being affected; then after another few days a second febrile reaction, similar to the four or five previously experienced, and still no visible vein was affected. While we were speculating as to where the inflammation would next appear there came a third similar attack, and the internal saphenous in the opposite groin became a whip-cord with accompanying œdema. From this point the process intermittingly measured off its length up the superficial epigastric vein to the breast and there ceased. Still another rest, chill and fever, and the same process entered upon its march along the course of the internal saphenous. It hitched along one six-inch length downward; halted; made a detour along the loop of external saphenous veins on the external aspect of thigh exactly as it did on the other side; ceased in this region in exactly the same way, measured off more and more lengths down the internal saphenous to the lower third of the leg, and ceased at the same level that it did on the first. When the inflammation made its appearance in the second leg all the lesion about the

veins of the first affected leg had disappeared; in like manner the perivascular tissues of the superior epigastric and the upper portion of the internal saphenous of the second leg had become quite normal.

When the process ceased at the right ankle and the lesion had disappeared the patient was well. She has since been well—more than two years.

Whether the perivascular lymphatics of the superior epigastric vein of the left side were inflamed before the patient came under observation can be only conjectured. There are reasons for thinking they had been, for the patient had complained of pain in the left hip and been ill some days before she collapsed in the art gallery. If then the inflammation behaved symmetrically in this respect as in all others, about two yards of superficial vein were involved first and last. The only hidden lymphatics affected, so far as known, were those of the pelvis along which the process advanced from the left side to the right in the interval of its ceasing at the left ankle and appearing at the right groin. As will be remembered, this progression was marked by two chills and two febrile reactions of the same degree of severity and of the same general character as those in the other steps of progression.

The treatment of the case consisted in rest in bed, elevation of the swollen limb (the second affected did not swell), fluid diet, general regulation of the functions of stomach and bowels. Local applications of various kinds were tried; cotton pads for protection; hot and cold, wet and dry applications, with and without pressure, for relief of pain and tenderness; but no specific treatment was attempted. No alkaline treatment was directed toward dissolving any intravenous clot, neither was any scarification attempted to limit the advance of the lymph-channel infection. Bichloride wet applications were attempted, but caused irritation, and were not continued systematically.

Quiet, rest in bed, fluid food, relief of symptoms, general good hygiene was the only aim in the latter stages. Nothing of the various plans of treatment tried at the outset seemed to modify the course, and the patient begged only to be left undisturbed.

It seems to the writer that periphlebitic lymphangitis is the correct name for the lesion in the present case. In the writer's experience the behavior of the tissues about superficial veins in typhoid fever has been practically the same. There has been the same whip-cord feel, tenderness, redness, œdema, and final subsidence of all evidences of previous inflammation. Furthermore, this inflamed tissue is located quite often upon limited lengths of vein, in continuity, spreading a

little or not at all, and disappearing, having apparently let loose no accidental emboli, and left no thrombosis. The masterful way in which so-called thrombo-phlebitis has been cured and veins restored, thrombus-free, suggests that the veins may have had a perivascular inflammation. A coat-sleeved infiltration, the perivascular spaces being crowded with lymphocytes, could easily give the cord-like feel, while yet the intimal coat and calibre remained practically undisturbed.

The writer cannot, at this point, refrain from expressing his opinion that infectious thrombo-phlebitis rarely, if ever, disappears completely, leaving a pervious vein. Upon this point discussion is invited.

As to the etiology of this variety of lymphangitis the explanation must await the results of animal experimentation or of chance autopsies. Bleeding piles, in the present case, would suggest themselves as a portal for entering infection. The infective process having appeared in the groin, its subsequent migration was along continuous ways, limiting itself to similar tissues. Why it confined itself for the most part to the lymphatics about the superficial veins, apparently selecting those of the internal saphenous and refusing those of the femoral; selecting those of the superficial epigastric and refusing those of the deep, is not easily explained. I have it on the authority of Professor George Huntington that the superficial veins are better supplied with surrounding lymphatics than the deep. Erysipelas has analogous characteristics and very similar features of appearance and behavior—*i. e.*, in cutaneous and subcutaneous tissues and surfaces.

Briefly to summarize:

An aged patient, without previous illness, suffered a migrating lymphangitis, which followed for the most part the course of superficial veins. There was no evidence that there was in any part a thrombosis, and the vein was ultimately left in an apparently normal condition.

Its infectious origin, intermitting advances, topographical limitations, suggest certain analogies of the process to that of erysipelas.

Again, the question arises just here as to the possibility and probability of an infectious venous thrombosis ever clearing up, leaving the vein quite normal.

The reason for calling attention to this case is the fact that the

migration was so extensive, and for the further reason that it seems to the writer that this lesion has been often set down by clinicians as phlebitis. Anatomists maintain that the perivascular lymph-spaces are not an essential part of the vein-wall. There may be no objection to the term "periphlebitis," but periphlebitic lymphangitis would seem to describe the lesion more completely.

SYPHILITIC NEPHRITIS.

By H. A. LAFLEUR, M.D.,
OF MONTREAL.

It is generally admitted that the visceral or internal lesions of acquired syphilis are the appanage of the latter manifestations, the so-called tertiary stage, of the disease. But while this statement holds good as a rule for the nervous system and the thoracic and abdominal viscera in general, an exception must be made in favor of the kidney, which at times becomes involved simultaneously with those tissues that bear the brunt of the early systemic infection.

The following three cases, which have come under my observation during the past two years, illustrate the question under consideration:

Case I. Male, aged thirty-eight years. When first seen at the out-patients' department of the Montreal General Hospital, December 30, 1893, he complained of pain in the left side of the chest, swelling of the legs, and a rash over the body. He was found to be in the secondary stage of syphilis, and this condition was associated with much œdema of the lower extremities and some puffiness of the face. His urine was turbid, reddish-brown and albuminous; the thick layer of sediment contained red and white blood-corpuscles in great number, and some epithelial and blood casts. He was subsequently admitted to the wards of the Royal Victoria Hospital, and I am indebted to Dr. James Stewart for the further history of the case. The patient had a very complete venereal record, having contracted gonorrhœa three times and soft chancres with suppurating bubo once. The last attack of gonorrhœa, which was complicated by double epididymitis, occurred about the beginning of November, 1893, and ten days after infection a sore appeared on the prepuce, followed at intervals of three and four days respectively by two others, all of which were healed in one month. Two weeks after the appearance of the chancres there was painless enlargement of the inguinal glands, and three weeks later a reddish eruption appeared on the forehead and body. Dropsy of the legs was first noticed in the last week of December. In November, 1893, he fell on a scantling, hurting his left side severely, and ever since had suffered pain in that situation. He gave an account of vague pains in the

body and limbs during the last fifteen years, but nothing to indicate articular rheumatism.

Physical Examination. Well-built, muscular man; face slightly swollen, a little lividity of lips. Prefers the sitting posture on account of pain in the left side. There is a rash of a brownish-red color, papular, and in some places papulo-squamous, distributed over the whole body, but especially marked on the forehead, upper part of the thorax, and thighs. On the upper extremities it affects principally the inner surface of the arm and the ulnar side of the flexor surface of the forearm. The individual papules vary in size from 3 mm. to 12 mm. in diameter. The inguinal, cervical and epitrochlear glands are enlarged and hard. There is an old scar in the left groin, and on the foreskin there are three small recent scars in the situation of the primary sores. The right testicle and the left epididymis are swollen and sensitive. Marked œdema of the legs exists from the knees downward.

Thorax. Mucous râles are heard at the bases of both lungs. The apex-beat of the heart is in the fourth intercostal space, about 1 cm. within the nipple line, and the cardiac dulness is within normal limits. There is roughening of the first sound at the apex, which may be either a short, rough, systolic murmur or a rapid reduplication of the first sound. Pulse 80, full and regular; respirations 20; temperature 98.4° F. Urine: slightly acid, specific gravity 1020, depositing a flocculent sediment, albuminous. (No note of microscopical character.) On January 12, 1894, mercurial inunctions were begun, and continued in five series until February 11th, a full bath being given every sixth day. The rash and the œdema gradually disappeared, and the patient was discharged well on the completion of the last series of inunctions. The quantity of urine passed daily varied between 1450 c.c. and 2800 c.c., increasing gradually to a maximum, and then diminishing.

Case II. A married woman, aged thirty-seven years, was admitted to the wards of the Montreal General Hospital on April 28, 1894, suffering from weakness, pains in the joints, and swelling of the hands and feet. About the end of January, 1894, while in New York, she began to have pain in the shoulder and extremities, which was worse in the morning on getting up, and abated during the day. She had fever, with slight chills and headache, and was confined to bed for a week. At this time a dull red rash appeared on her body and extremities, without any pain or itching. The articular pains left her in about a week, and she came to Montreal. In the second week of April, *i. e.*, about two months and a half from the appearance of the rash, her hands and feet became swollen, and there was a return of the headache, with pains in the finger-joints and right ankle. She had lost a good deal in weight. No mention was made of urinary symptoms. She had never had articular rheumatism, and had no knowledge of specific infection in herself or in her husband. Her last child was born four years ago, and she had had no miscarriages.

Physical Examination. Large woman; complexion sallow, lower eyelids puffy, mucous membranes a little pale. From the knees downward the legs

are swollen, pit on pressure, and are slightly sensitive. The hands and wrists are also slightly swollen and painful on pressure. There are no definite articular swellings. The whole surface of the body is covered with a discrete, pale, dusky-red, flat papular eruption, which is most abundant on the trunk and the flexor surfaces of the upper extremities. It is less evident on the face, and on the palms of the hands is macular. The individual papules are from 1½ to 5 mm. in diameter. A few are capped with fine branny scales, and the skin beneath them is distinctly felt to be infiltrated. There are painless nodular enlargement and induration of the inguinal, epitrochlear and cervical lymphatic glands. Nothing abnormal is seen in the throat, and there is no falling of the hair. Pulse 72, of good volume; no increase in tension. Heart: apex-beat within the nipple lines; deep dulness above the fourth rib, laterally from mid-sternum to the apex. There is a lengthening and roughening of the first sound, most distinctly heard at the apex, less so over the rest of the præcordial area. A few mucous râles are heard at the base of the right lung. Urine: turbid, smoky in color, faintly alkaline, specific gravity 1012; deposits an abundant, curdy, reddish-brown sediment. Large amount of albumin. Urea, grs. iv to the ounce. Microscopic examination of the sediment from a quantity of urine drawn by catheter shows a great number of red and white blood-corpuscles, some brownish-red blood-casts and a few hyaline casts. The treatment consisted in rest in bed, an exclusively fluid diet, and the administration of one quarter grain of the protoiodide of mercury three times daily. The amount of urine passed daily varied in the first week from 900 to 1250 c.c., in the second week from 1000 to 1300 c.c., in the third week from 1500 to 2150 c.c., in the fourth week from 1620 to 2300 c.c., in the fifth week from 1300 to 2000 c.c., and in the sixth week from 1300 to 1780 c.c.

The course of the illness was afebrile throughout. The œdema soon disappeared, the rash more slowly, leaving yellowish-brown discoloration of the skin. Albumin and cellular elements in the urine diminished gradually, the red blood-cells being the first to disappear. The patient was discharged well on June 4th, the urine having been free from abnormal constituents for many days. She had gained in weight, and showed no signs of any organic disease. I have seen her since she left the hospital; she remains in good health.

To recapitulate: both of the patients whose histories I have given above were the subjects of constitutional syphilis, one of them giving a clear history of primary infection, and both coincidently with a papulo-squamous syphilide and ganglionic enlargement developed œdema, albuminuria, and hæmaturia. There could be no question of simple passive congestion of the kidneys, for there was no evidence of venous stasis in the other viscera or of organic disease of the heart or lungs to account for such a condition. In both cases there was a true nephritis, and the only etiological factor which could be demonstrated was syphilis.

In a third case, that of a married woman I saw in consultation with Dr. Deeks, of Montreal, but of which I have no detailed notes, there was a history of infection from the husband, who had well-marked syphilis. About six months after the appearance of a syphilide the woman became dropsical with albuminous urine, and four months later, when I saw her, the condition was practically the same. The œdema had lessened, but the urine was highly albuminous, and contained red and white blood-cells and some casts.

Such a nephritis finds its analogue in the renal disease which accompanies or follows other infective diseases, notably scarlatina, diphtheria, smallpox, typhoid fever, erysipelas, and malaria.

It is remarkable, considering the prevalence of syphilis, that this subject has not attracted attention until a comparatively recent time. While the relation of syphilis to amyloid degeneration in the kidney has long been known, the effect of the syphilitic poison on the kidney in the earlier stages of the disease escaped recognition for a long time. Even at the present time there is no mention of the occurrence of acute nephritis in the secondary stage of syphilis in medical works in the English language that I know of, with the exception of an excellent article in Morrow's *System of Genito-Urinary Diseases, Syphilis and Dermatology*. A very complete account of this condition is to be found in the *Traité de Médecine*, edited by Charcot, Bouchard and Brissaud. Gregory Wells and Blackall at the beginning of the present century noted the occurrence of albuminuria in syphilitics, and attributed it to the use or abuse of mercurials. To Rayer, in 1840, belongs the credit of showing that the medicinal use of mercury did not produce albuminuria, and of the opinion that this symptom was due to the action of the virus of syphilis itself. The first mention of an affection of the kidney in the early secondary stage of syphilis was made by Jaccoud (*Leçons de Clinique Médicale*, 1867, p. 712). He remarks that it would be an error to suppose that renal involvement occurs only during the tertiary stage, and cites two cases of albuminuria, accompanied by epithelial and hyaline casts in two women who were the subjects of secondary syphilis, and in whom mercurial treatment brought about a speedy cure after iodides had completely failed. He considered, however, that the condition was one of early amyloid degeneration. Perroud, of Lyons, in 1867, gave the first accurate account of two cases of early syphilitic albuminuria.

Subsequently contributions to this subject were made by Descouts (Thesis, 1878); Drysdale, of London (1879); Négel (Paris Thesis, 1882), who collected prior observations; Cornil and Brault (1883); Mauriac (1890); Lecorché and Talamon (1891); Petersen, of St. Petersburg (1891); Géraud (1892); Darier, Barthélemy, and Jaccoud (1893).

The proportion of syphilitics in whom the kidney is affected during the secondary stage is estimated to be about 3.8 per cent. (Petersen.) The involvement of the kidney occurs usually from two and a half to three and a half months after the appearance of the initial lesion, but in some cases is delayed until the sixth month, or even later. In Mauriac's series of twenty-three cases the extremes were four weeks and three years respectively, but it is very doubtful if the latter case should not be classed rather as an example of early amyloid degeneration. Of the three cases I have mentioned, the initial lesion could be traced in the first only, and in this case the interval between the chancre and the onset of nephritis was a little over six weeks. The nephritis supervenes in a majority of the cases at the time the roseola makes its appearance, or shortly after; but instances are recorded in which albuminuria preceded the syphilide.

The onset is insidious, without prodromata, or with merely lassitude and slight lumbar pains. There is sometimes a trifling elevation of temperature, but as a rule the course is afebrile throughout. Nearly always œdema is the first indication of the renal trouble. It sometimes affects first the eyelids or some part of the face, and extends slowly or rapidly to the legs and genitalia, or occurs in the reverse order. In any case it may become general, and though liable to oscillations, proceed to an extreme degree, and be accompanied by effusions into the serous sacs. There is usually pallor of the skin and mucous membranes, and the general aspect is often similar to that seen in the subacute forms of nephritis coming on after exposure to cold. Albuminuria is constant, and the quantity of albumin passed daily varies from fifteen to twenty grammes, or even more. At first a normal, or almost normal, quantity of urine is passed, the quantity diminishing gradually, and the urine becoming cloudy, pinkish-red, then dark-red, smoky, and depositing a more or less copious dark-red sediment. The urea is diminished. The sediment shows, as in the cases related above, a preponderance of red and white blood-copuscles, with some

epithelial, blood, hyaline and granular casts. If the course of the illness be favorable there is a gradual increase in the flow of urine, and as gradual a decline to the normal, the formed elements meanwhile becoming fewer, the red blood-cells being the first to disappear. There are often no subjective symptoms except those produced by the dropsy. Seldom is frequency of micturition complained of, or pain in the region of the kidneys. The graver phenomena of urinary toxæmia are only exceptionally seen, and then most frequently in the gastro-intestinal form, but temporal headache is not uncommon in mild cases. Coma, convulsions, disturbances of vision, and cardiac asystole are rare.

The protracted and fatal cases, which may often show relapses, are marked rather by extensive anasarca, serous effusions and gastro-intestinal symptoms, and in this respect closely resemble fatal cases of subacute nephritis *a frigore*.

The nephritis lasts on an average about five weeks, and usually ends in complete recovery, but may be prolonged to four or five months, especially if specific treatment is not tolerated, or if relapses occur, as not infrequently happens. In some cases albuminuria persists for months without any other symptoms, and finally disappears. More rarely it is permanent, and is the precursor of chronic Bright's disease. Rapidly fatal cases of syphilitic nephritis have been recorded; in Darier's case death occurred after an illness of twenty days, and in Barthélemy's at the end of a fortnight.

There should be no difficulty in establishing the diagnosis of syphilitic nephritis if the patient presents the combination of well-marked signs of secondary syphilis with unequivocal evidence of nephritis, provided that it is established that there was no antecedent renal disease. The almost constant absence of any other ascertainable etiological factor, moreover, justifies at least a provisional diagnosis, and the usually rapid and complete subsidence of the trouble under specific treatment is the best proof of its dependence on luetic infection, such treatment having no appreciable power for good in non-specific cases. Difficulty in diagnosis may arise when there are no actual specific lesions present, as in the cases in which the onset of nephritis is delayed beyond the usual period, when the cutaneous lesions are scanty and ill-defined, or when, as remarked above, the nephritis precedes the syphilitic rash. Géraud mentions two cases in which there were suspicious ulcers, and the diagnosis of syphilis was made before the

appearance of the roseola from the presence of albumin in the urine. I venture the suggestion that just as in scarlatina, where a nephritis may be the only evidence of the action of the virus, so in syphilis an acute inflammation of the kidney may be the only visible effect of specific infection.

The essential point in the treatment is the administration of mercury. It is generally immaterial in what form mercury is given, though in severe and rebellious forms of secondary syphilis it is advisable to get the patient under the influence of the drug as rapidly as possible. It should be remembered, however, that when the kidney is affected stomatitis is more easily produced than usual, and this fact has led Petersen to remark that when the gums of syphilitics are readily affected by mercurials, attention should always be directed to the kidneys.

The general and dietetic treatment differs in no respect from that of acute or subacute nephritis due to other causes.

Owing to the small number of fatal cases recorded, there are not many observations on the pathological anatomy of syphilitic nephritis. The lesions are in the main those of a glomerulo-nephritis. Cornil and Brault described the lesions found in two cases as follows: The kidneys are enlarged, smooth, and weigh from 225 grammes to 290 grammes. The surface is grayish-white or grayish-red, and the stellate veins are well-marked. The capsule strips off easily. The kidneys are firmer and offer a greater resistance to the knife than do the normal organs. The cortex is thickened and pale, contrasting strongly with the dark-red medullary portion. Microscopic examination of sections of the cortical portion shows that the chief changes are in the glomeruli and the arterioles. The loops of the glomerular tufts present a marked thickening with proliferation of the epithelium covering them. The cells of Bowman's capsule are increased in number and crowded together in an irregular fashion. Some fatty degeneration is seen in sections stained with osmic acid. Around the glomeruli are tracts of newly-formed connective tissue, separating the atrophied tubules and joining other similar tracts around the arterioles. There are also, irregularly distributed in the cortical areas, a small-celled infiltration of lymphoid elements and collections of polynuclear leucocytes, especially beneath the capsule of the kidney. Many of the arterioles show an obliterating endarteritis. The convoluted tubules

are dilated and contain coagulated exudation in some cases; in others there is no appreciable change. Changes in their lining epithelial cells are not constant; if present, they consist in cloudy swelling and dropsical or fatty degeneration. Various bacteria have been found in sections of the kidney and in the urine in similar cases.

None of these lesions have any specific character; they resemble those of the nephritis following scarlatina, malarial infection or exposure. This is no reason, however, for denying their dependence on the action of the virus of syphilis; for the diffuse hepatitis which accompanies gummata in the liver, certain forms of arteritis, and chronic osteitis and periostitis, all of which are known to follow luetic infection, have not themselves any specific character. The chief conclusions to be drawn from a study of this subject are that syphilis is an etiological factor in a considerable number of cases of acute or subacute nephritis, and that in all cases, in view of the prognosis and treatment, a careful investigation should be made as regards actual syphilitic lesions, or a possible antecedent syphilitic infection.

THE USE OF DISPENSARIES IN TEACHING.

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It is not the purpose of this paper to deal with the pernicious multiplication of dispensaries, but to call attention to what appears to be the best manner of utilizing for teaching purposes the patients who attend the outdoor service of the hospital of every medical school.

It has been my privilege to have been connected with the out-patient department of the Hospital of the University of Pennsylvania ever since I graduated in medicine. Until the last few years the dispensary service was viewed as a good school of practice for the gentlemen in charge and was used by them for instruction of their private students, and for the purpose of feeding the wards and the clinical lecture-room. Much good work has been done there, but no routine use of the patients was made until Professor Tyson took the Chair of Clinical Medicine. At that time the classes were so large and the ordinary material used was so scarce that it became necessary to utilize all the available material, and the medical dispensary was forced into the service.

In order that the material could be used to advantage, numerous changes became necessary, which have not only produced a good teaching service, but have enhanced the value of the clinic for purposes of observation. I am aware that much the same plan is used at other institutions, notably the Johns Hopkins Hospital, from which institution we copied the plan of cards, but it has not seemed necessary to go into a comparison of methods, but rather to describe a valuable plan.

The service is in charge of a chief and four assistants, two clinical assistants, a recorder, and a microscopist.

The duty of the *recorder* is to take the histories of all cases. This not only hastens the work by saving time to the clinical assistant, but

a very thorough history is obtained. A set of stereotyped questions is asked of all patients, so that the histories are of value for comparison. The histories are taken on cards 7 by 7 inches (Fig. 1), instead of

FIG. 1.

Whole No.——— *Medical No.*———

University of Pennsylvania Medical Dispensary.

Name ——— *Age*——— *Race*———

Condition ——— *Occupation*——— *Admitted* ———

Diagnosis———

Family History———

———

———

Previous History———

———

———

———

using a book, which allows the patient to be taken to any part of the building, accompanied by his history, without interfering with the histories of the other cases. These cards are numbered, and filed according to the number. The patient's name and number are then taken on a smaller card, which is indexed alphabetically; besides these two cards the patient is given an ordinary dispensary card bearing his name and the number of his history. (Fig. 2.)

FIG. 2.

Nam ———

No. ———

MEDICAL DISPENSARY.

After the histories have been taken by the recorder the patients are transferred alternately to the two clinical assistants, who make a

thorough physical examination of every case, whatever the history. They also prescribe the proper treatment, and order the examination of blood, etc., where necessary. There are two clinical assistants, because too much time would be consumed if there was only one man to do all this work.

The duty of the microscopist is to examine the urine of *all* patients, the sputum, if the patient has a cough, the blood, and the stomach contents.

The chief has general supervision, being consulted especially in all new cases, and in those of unusual interest.

This machinery may seem cumbersome in the reading, but works without a hitch. Each patient is given a thorough examination, so conspicuous by its absence in the usual dispensary. Many cases of unsuspected disease are discovered, and, I believe, but few patients get away without their condition being recognized, and above all, perhaps, it makes the material available for ward-class purposes.

Two methods are used in teaching the ward classes :

The class is divided into several subsections, each subsection being in charge of an instructor of clinical medicine, each subsection going in turn to the medical dispensary. Here each class is divided into two groups and each group given a patient for examination. Preferably a patient is chosen who has never before been to the dispensary.

In using the first plan the students are themselves required : first, to take a good history, to facilitate which they are supplied with the same set of questions used by the recorder; second, to make their own physical examinations; third, to endeavor to arrive at a diagnosis ; and, fourth, to suggest treatment. In all this the instructor is merely a mentor, pointing out the best methods of procedure, but being careful to allow the students to do the work themselves. After the students have made their diagnosis the instructor goes over the case with them, points out the mistakes which they almost always make, shows them their omissions, and revises the treatment. The awkwardness which marks the handling by the students of their first case and the quickness with which they learn to go about the work prove at once the advantage of allowing the student to come in direct contact with the patient without the intervention of an instructor.

The second plan used, which is utilized only when patients are scarce, is for the recorder to take the history as usual ; the patient is

then sent to the ward class, where the instructor goes over the case, points out the various lesions, and dilates upon them more or less fully.

The superiority of the first plan is, I think, manifest. It brings the student in direct communication with the patient, it forces him to depend upon himself, and it brings him face to face with the patient, just as he will be in the consulting-room after graduating. Surely the more of such practical experience a student has before he leaves college the fewer initial mistakes he will make.

Again, it saves him from a clinical lecture by the instructor. A ward class, I take it, should be used to familarize the student with the methods and instruments used in making a diagnosis, not the least important of which is the taking of a history and with the lesions found in diseased conditions. A lecture should be reserved for a clinical lecture-room, its proper place, and not be indulged in by the instructor. An advantage of selecting a patient who is new to the instructor as well as to the students is that it sharpens his powers of observation, forces him to make a thorough examination of all the organs, instead of dilating upon the most attractive lesion, or treating simply for the symptoms complained of. He is bound to do this if he does not desire to be tripped up, for there is no body of men who delight in catching their instructors in a mistake more than the medical students.

When dispensary teaching supplements the clinical lecture, and is in turn supplemented by the opportunity to examine a series of cases, such as heart lesions, lung lesions, etc., in the wards, I take it we will have the ideal method of teaching I have described.

While the method, or some variations of it, is used in some institutions, I am quite sure its use is not general enough. Usually an interesting case is selected and its special points shown, the ordinary cases of dyspepsia, bronchitis, etc., are entirely ignored for teaching purposes, and a student heretofore has frequently left college without ever having seen a case of dyspepsia or bronchitis, except from the benches of the clinical-room. Again, the negative results of a physical examination in these cases is just as advantageous to the student, even more so, than the discovery of a heart murmur or a consolidation ; for then he will be taught that all cases of palpitation of the heart are not due to organic heart disease and that all coughs are not due to phthisis.

MESCAL BUTTONS.

ANHALONIUM LEWINII—HENNINGS. (LOPHOPHORA WILLIAMSII-LEWINII—COULTER.)

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THE study of Anhalonium Lewinii is of comparatively recent date, the subject having been brought to the attention of the medical world in 1888 by Dr. Lewin, of Berlin, who published at that time the results of his observations upon the drug. In 1894 Drs. Lewin and Heffter, of Germany, reported the results of further study of the subject. In 1891 James Mooney, of the United States Bureau of Ethnology, in a paper read before the Anthropological Society of Washington, first brought to public attention the remarkable religious ceremonial use of the plant by the Kiowas and other tribes of the southern plains, among whom he had been conducting researches for some time. In 1894 he brought back to Washington for examination a large quantity of mescal, under the belief that investigation would corroborate the claim of the Indians as to its valuable medicinal properties. This was given over to Mr. E. E. Ewell, of the Department of Agriculture, for chemical analysis, and to the writers for therapeutic test.

Our study of the subject has shown that the mescal buttons possess properties which are remarkable, the exact likeness of which is not found in any other known drug, and also that it possesses virtues which, when applied in the treatment of certain diseased conditions,

may prove the drug a valuable addition to our present list of therapeutic agents. It is for these reasons that we have chosen to present this subject in this paper for your consideration.

Anhalonium Lewinii is a plant belonging to the natural order of *Cactaceæ* or Cacti, as they are commonly called. One of the divisions of this great order is the genus Anhalonium, of which there are several species, and among them *Anhalonium Williamsii* and the one now under consideration, *Anhalonium Lewinii.*

As to the exact place in the botanical classification which the Anhalonium Lewinii should occupy there is some difference of opinion among botanists. Hennings,[1] who first published an accurate description of the plant, believed it to be a separate species of the genus Anhalonium. Dr. A. Heffter[2] holds the same view, reasoning both from botanical characteristics and the dissimilarity in physiological action between the A. Williamsii and A. Lewinii. On the other hand, botanists who have investigated the subject more recently hold that the A. Lewinii is but a variety of the species A. Williamsii. Coulter, an authority upon the cacti, holds this view and gives the plant the name Lophophora Williamsii-Lewinii.[3] The botanist in charge of the United States Botanical Gardens in Washington believes that the two plants belong to the same species.

The Anhalonium Lewinii inhabits portions of the valleys of the Rio Grande and Pecas Rivers in Texas and New Mexico, growing in barren rocky soil, and often in places which can be reached only with difficulty by those who gather it. It reaches a height of about one inch above the surface of the ground. The body (Fig. 1) is comparatively thick, and is surmounted by a top, which is composed mainly of the blunt leaves of the plant. In the centre of this top is a tuft, about one-half to one inch in diameter, composed of yellowish-white filaments, or hairs. These tops, when dried, constitute the mescal buttons, the commercial form of Anhalonium Lewinii.

The mescal buttons (Fig. 2) are of a brown color, circular, about one-half to one and a half inches in diameter and one-fourth of an inch in thickness. The edge curls upward, giving the under surface

[1] Therapeutic Gazette, 1888.

[2] Ueber Pellote: Arch. f. Exper. Path. u. Phar., 1894. xxxiv. 65.

[3] J. M. Coulter: Preliminary Revision of the Cacti. Bulletin U. S. Department of Agriculture, Washington, 1894.

a convex appearance. In the centre of the upper surface is a tuft composed of the yellowish-white hairs before mentioned, and matted down so as just about to reach the level of the upturned edge. The buttons vary in weight from about one to eight grams, the average being about four grams.

The button is somewhat brittle and hard, and can be pulverized in a mortar with difficulty. In the mouth, however, under the action of the saliva, it swells and rapidly becomes soft, the consistency which it acquires giving somewhat the sensation imparted by slippery elm. The taste is disagreeable and nauseous, and very bitter, with a persistent after-taste. A marked sensation of stinging or tingling is produced in the fauces, which remains for some time after the drug has been swallowed. The powdered drug is odorless when dry, but acquires a nauseous odor upon being moistened.[1]

PHYSIOLOGICAL ACTION. In connection with the physiological action of the mescal, its use by the Indians is of great interest. The Kiowa Indians and their associated tribes, formerly ranging from the Arkansas River southward into Mexico, have, from the earliest period, made its use a regular part of their religious ceremonies. When finally gathered upon the Kiowa Reservation in Oklahoma, which they now occupy, they continued the use of the buttons in their ceremonies, the demand being supplied by traders who obtain it from the valley of the Rio Grande. Its use has spread to such an extent that the rite has become the chief religion of all the tribes of the southern plains. Complaint being made to the governmental authorities at Washington by missionaries and others, the eating of the drug was rendered unlawful and was forbidden under severe penalties. Nevertheless, the use of the mescal has persisted to the present time.

The religious ceremony, as described by Mr. Mooney, who has participated in it several times, usually takes place on Saturday night. The men seat themselves in a circle within the tent, around a large fire, which is kept burning brightly. After a prayer the leader hands each man four buttons, and each having been freed from the tuft of hairs is put into the mouth, and, after it is thoroughly softened, is ejected into the palm of the hand, rolled into a bolus, and swallowed. At midnight each man calls for as many mescals as he wants, and in

[1] The writers in Therapeutic Gazette, September, 1895.

this way ten or twelve of the buttons, as a rule, are taken at intervals between sundown and daybreak. They sit quietly throughout the ceremony, while the fire is kept burning brightly, and a continual singing and beating upon the drum is kept up. Most of the time they are in a state of reverie, the intoxication of the drug showing itself in the visions of color and other manifestations, which will be described later. The hours are interspersed with songs, prayers for the sick, and baptismal rites. They sit thus from sundown to nearly noon of the next day. At the close of the ceremony they go out, it is claimed, without the slightest depression or unpleasant after-effect. Upon the day following the ceremony they carefully abstain from the use of common salt with their food; this, it seems, for a religious reason, and not because of any incompatibility of salt with the drug or its effects.[1]

To determine the physiological action of the crude drug—the mescal buttons themselves—upon the human system, they were administered in varying quantity to different young men who kindly volunteered their services for the purpose. Eight of these experiments were made, and in each enough of the drug was given to produce decided characteristic symptoms. Observations were taken at frequent and regular intervals to ascertain the effects upon the different portions of the body. Most of these experiments have been reported in full,[2] but time does not permit us to give a detailed account of them. The following are, briefly, the results obtained:

The most remarkable of the physiological effects of the drug was the production of visions. These appeared in most cases after three of the buttons had been taken. The visions ranged from ill-defined flashes of color to most beautiful figures, forms, landscapes—in fact, there seemed to be absolutely no limit to the variety of visions which the drug could produce. They could in but few instances be seen with the eyes open, but upon closing them an ever-changing panorama appeared. Drumming, or otherwise marking regular time, had a marked effect upon the visions, much enhancing the beauty and variety of the objects seen. This fact is of interest in connection with Mr. Mooney's statement, that during the eating of the mescal by the Indians there is kept up a continued beating upon the drum. In

[1] See also "Mescal Plant and Ceremony." J. Mooney. Therapeutic Gazette, January, 1896.
[2] Therapeutic Gazette, September, 1895.

three cases the visions were under the control of the will, and in two they were subject to the suggestion of others. The effect of the drug in the production of visions is probably due to stimulation of the centres of vision in the brain. The persistent ache and feeling of exhaustion in the occipital region, which persisted for several days after one of the experiments, is of interest in this connection.

A clearer idea of the nature of these visions is given by the following extract from one of the cases already reported. In all other cases similar effects were produced:

> The first sensations that followed my taking the drug came upon thoughtlessly closing my eyes. Instantly there sprang into the field of view a host of little tubes of shining light, down which green and red balls the size of peas were constantly rolling. The tubes of light bent themselves into the shape of letters, but they would spell nothing, and, slowly curving themselves into grotesque shapes, began to revolve rapidly, the green and red balls going in the opposite direction with even greater velocity. All the field of view between these silent wheels was filled in with a shifting mass of green. The colors were wonderful. They were the colors of the spectrum intensified as though bathed in the fiercest sunlight. No words can give an idea of their intensity or their ceaseless, persistent motion. The figures constantly changed in form and color, but always remained a series of fantastic curves, revolving rapidly back and forth upon their own axis. The forms changed through rich arabesques, Syrian carpet patterns, and plain geometric figures, and with each new form came a new flush of color, every shade appearing, from pure white to deepest purple. When the eyes opened and the light was turned up, the visions faded like stars going out in daylight, and the room, tables, chairs, and all the surroundings came back into real existence and within the reach of the hands.

It will be seen that the predominating hallucinations are the wonderful color phenomena, although the figures, forms, etc., are in themselves sources of pleasure and admiration.

In some cases no effect whatever was produced upon the reason or will of the individual. In others, there were some slowness of thought and loss of power of expression, and, in one of the experiments, a marked delusion. Compared with other drugs of this class, however, the effect upon the mind is extremely slight.

Dilatation of the pupil was well marked in every case, and persisted for from twelve to twenty-four hours after the drug was taken. The dilatation was accompanied by a slight loss of the power of accommodation and consequent disturbance of vision.

More or less depression of the muscular system existed in every case, and this was the first effect noticed after the drug was taken. It ranged from a feeling of lazy contentment to marked muscular depression. Susceptibility to this effect varied widely. Whether the sedative effect is produced by action on the nerve-centres, peripheral nerves, or their nerve-endings, or on the muscular fibres themselves is yet not determined, but indications point to action through the nerve-centres.

Partial anæsthesia of the skin was present in three of the cases, appearing when the effects of the drug began to wear off.

The heart action is at first rendered slower and stronger. This is followed by a rise to the normal, which continues during the period of greatest activity of the drug. In the cases in which the muscular depression was greatest, slight, if any, depression of the heart was present.

The respiration was unaffected in all cases but one. In this it seemed to partake slightly of the general muscular depression.

Upon the stomach the drug produced an effect which varied from a feeling of uneasiness and fulness at intervals to nausea and vomiting.

Inability to sleep for at least twelve hours after the influence of the drug passed off was a uniform effect.

Appreciation of the duration of time was lost in all cases—as in the effect of cannabis indica. In one case a snowstorm appeared to last an hour, although, in fact, the vision continued not more than one minute.

No constant effect upon the bowels, skin, temperature, and the amount of secretion of the various glands of the body was found.

The only record of the taking of Anhalonium Lewinii for experimental purposes which we have been able to find is that of Briggs.[1] He took "a third of a specimen," and the symptoms produced were the following: In fifteen minutes the pulse rose from 60 to 70. In thirty minutes there was fulness of the head, pulse 90, respiration 26. The sense of fulness increased, and was followed by a headache and swimming in the head. Suddenly the pulse shot up to 160, and the respiration increased so that he could with difficulty get sufficient breath to keep himself alive. He thought he was about to die, and became unconscious. In six to eight hours his pulse and respiration

[1] Lewin: Archiv für Experimentelle Pathologie und Pharmakologie, Band xxxiv., Heft 5 u. 6.

went down again to the normal. Great depression existed for twelve hours.

The symptoms produced in this experiment are so widely different from those which we have obtained from administration of the drug that we cannot believe that the drug taken by Briggs was the same one which we have now under consideration.

Lewin,[1] in experiments upon animals, found that in them the drug produced an acute muscular spasm of varying intensity, with increased reflexes, its action in this particular much resembling strychnine or brucine. No such effect was present, however, in our experiments upon man. Whether or not it would be produced by much larger doses is, of course, a matter of conjecture. In some animals, also, a quickened respiration was noted, which effect was present in our experiments only in one case, and in the presence of great general muscular depression. In animals, also, the heart remained unaffected, whereas, in man, we found a primary slowing of the heart action. In both animals and man more or less tendency to nausea and vomiting existed in most cases.

The physiological action of Anhalonium Lewinii upon man cannot be said to be identical with that of any other known drug. Its effects resemble those of certain drugs in some of the symptoms produced, but differ widely from them in others. Cannabis indica produces visions, with dilated pupils, and with slight effect upon the circulation. In these particulars its action is similar to Anhalonium Lewinii. But cannabis indica is an hypnotic, and the delirium and hallucinations are in most cases followed by sleep. Anhalonium Lewinii, on the other hand, tends to produce wakefulness in every case. The Indians do not sleep for twenty-four hours after the commencement of their ceremony, and in our experiments sleep was found to be impossible for about the same length of time.

In this tendency to produce wakefulness it resembles cocaine. The visions produced by cannabis indica "are generally of a gay character, producing much merriment, accompanied by a great inclination to muscular movement."[2] The visions of Anhalonium Lewinii provoked wonder and admiration, but no merriment, and there was present disinclination to make any muscular effort. Other marked differences

[1] Archiv für Experimentelle Pathologie und Pharmakologie, Band xxxiv., Heft 5 u. 6.
[2] Brunton: Pharmacology, Therapeutics, and Materia Medica, p. 1026.

exist which will become evident to anyone comparing the action of the two drugs.[1]

ALKALOIDS OF ANHALONIUM LEWINII. In 1888 Lewin subjected the mescal buttons to chemical analysis, and succeeded, by chemical methods which need not be given here, in obtaining an alkaloidal substance, to which he gave the name *anhalonin*, and to which he ascribed the chemical formula $C_{12}H_{15}NO_3$. Mr. Ewell,[2] who has succeeded in obtaining anhalonin in a pure state, describes it as a white, strongly alkaline substance. It crystallizes from aqueous solution in prismatic, sometimes tabular crystals of the rhombic system. It is soluble in a large quantity of water, and is unusually soluble in alcohol, ether, chloroform, benzine, and petroleum ether. Its melting-point is 77.5° C., and it can be sublimed without decomposition. It forms salts with the ordinary acids.

Anhalonin hydrochlorate (Fig. 3), which was used in our experiments with the first alkaloid, is a white, odorless substance, forming needle-like crystals. It is soluble in water in the proportion of 2 parts per 100. The solution is very bitter to the taste. The hydrochlorate is also soluble in alcohol. It melts at 254°–255° C., with decomposition. It rotates the plane of polarized light to the left. Lewin describes an amorphous as well as a crystalline hydrochlorate, but, in the opinion of Mr. Ewell, the former is but an impure hydrochlorate.

Lewin[3] describes *anhalonin sulphate* as forming needle-like crystals, colorless or of a slightly yellowish tinge; easily soluble in water, but much more so in hot water; almost insoluble in alcohol and ether.

The physiological action of anhalonin upon guinea-pigs and other small animals has been investigated by Lewin and Heffter. Lewin found that in these animals the alkaloid produced at first a primary collapsed condition, which was followed by an increase in the reflex excitability, and, if the dose administered were large enough, convulsions, which resembled, to a certain extent, those produced by strychnine. The action of the drug, as far as these experiments would indicate, is somewhat analogous to strychnine. The lethal dose was found to be 0.16 to 0.20 gm. per kilogram of body weight.

[1] The writers in Therapeutic Gazette, September 16, 1895.

[2] I am indebted to Mr. E. E. Ewell, Bureau of Chemistry, United States Department of Agriculture, for the chemical description of the constituents of mescal buttons and the photographs reproduced in this article.

[3] Archiv f. Exper. Path. und. Phar., 1888, xxxiv. 401.

These results we have verified by a series of experiments upon guinea-pigs in the laboratory. The following experiment is fairly typical:

Guinea-pig, weight 425 grams.
1.01 o'clock. Injected 0.05 gm. anhalonin hydrochlorate in solution.
1.03. Tremor.
1.05. Tremor of whole body. Opisthotonos, followed by convulsion.
1.08. Slight convulsions. Pulls itself around by front legs—hind seem paralyzed. Opisthotonos.
1.10. Convulsion on touch.
1.12. Breathing rapid. Tremor of front extremities.
1.15. Attempts to move, but cannot, except extremities.
1.20 to 1.40. Constant convulsive movements of whole body, normal reflex to touch, breath of air, sound, etc., exaggerated.
1.30. Biting and chewing. Opisthotonos.
1.40. On feet. Condition better. No tremor or convulsions.
1.45. Convulsions, precipitated by rubbing back. After it, legs extended for a short time.
1.47. Sits up. From this time gradually improved.

In order to ascertain the action of anhalonin upon man Dr. Morgan took the drug in progressively increasing doses daily up to 0.20 gm. without any appreciable effect. As this amount is nearly four times the quantity of anhalonin contained in the crude drug administered in the experiments already reported, it is evident that anhalonin cannot be the active principle of mescal buttons, or even a potent factor in the production of their effects.

A second alkaloid has also been obtained from A. Lewinii,[1] and was called by Heffter alkaloid B. This, for convenience, we shall call *mescalin*. Its formula, crystalline form, solubility, etc., are now being made a subject of study by Mr. Ewell. It is soluble in ether, chloroform, and petroleum ether. In the last it is much more sparingly soluble than is anhalonin. It forms a hydrochlorate when brought into contact with hydrochloric acid.

Hydrochlorate of mescalin is a white substance, forming tabular crystals. It is much more soluble in water and alcohol than is anhalonin hydrochlorate.

We have conducted a series of experiments upon guinea-pigs to de-

[1] Dr. A. Heffter: Arch. f. Exper. Path. und. Phar., 1894, xxxiv. 65.

termine as nearly as possible the characteristic effects of mescalin, and in what particulars its action differs from anhalonin.

I. Guinea-pig, weight 576 grams.

0.01 gm. mescalin hydrochlorate, in solution, hypodermically. No appreciable effect.

Later, 0.02 gm. injected into same animal. No decided effect.

Seemed more sluggish in movement, and less easily frightened than normally. Breathing more rapid.

II. Guinea-pig, weight 425 grams.

12.15 o'clock. 0.03 gram mescalin hydrochlorate hypodermically into inner side of thigh.

12.19. In corner. Apparently drowsy. Not move when struck.

12.23. Tremor of head and body.

12.28. Most rapid convulsive movements of extremities, as if running, but made little progress, as feet seemed to take no hold upon floor.

12.30. Quiet on belly, in natural position.

12.43. Same. Seems drowsy. Recovery from this time.

III. Guinea-pig, weight 416 grams.

12.53 o'clock. 0.04 gm. mescalin hydrochlorate, in solution, hypodermically.

12.57. Runs around uneasily. Rapid chewing movements of jaw.

12.58. Pupil slightly dilated. Chews rapidly. Tremor of head.

12.59. Runs around in frightened manner, with tremor of body. Chews. Breathing rapid.

1.00. Runs around, jumps high, and falls on side in convulsions. Extremities stiff. Opisthotonos.

1.01. On feet again. Tremor. Breathing rapid.

1.02. Pupil dilated. Breathing rapid and labored.

1.05. Violent convulsion.

1.06. More quiet. Tremor.

1.11. Looks around more normally. Breathing 150 per minute and difficult. Shakes whole body.

1.16. Moves backward. Breathing same.

1.20. Breathing 120 per minute. Walks backward.

1.33. Runs backward around cage.

1.40. Breathing 104, but more irregular.

2.10. Walks backward. Breathing much slower, but weak and irregular.

3.00. Animal bright and will run forward when touched suddenly.

Recovery.

IV. Guinea-pig.

1.00 o'clock. 0.047 gram mescalin hydrochlorate, in solution, hypodermically.

1.03. Frightened and restless. Breathing rapid.

1.04. Rapid chewing movement at intervals.
1.05. Very restless. Tremor in moving. Respiration irregular and labored.
1.06. Runs around at intervals.
1.08. Jumps up and falls on side in convulsion. Extremities rigid.
1.08½. Gasping on side.
1.10. Respiration ceased.
1.13. Thorax and abdomen opened. Auricles and ventricles found beating, but not synchronously. Auricles beating rhythmically at 60 per minute. Ventricles, 26 per minute.
1.27. Ventricles, 24 per minute, and very weak. 2 drops 10 per cent. solution mescalin hydrochlorate dropped on heart. Beats become more rapid and stronger than before, and continue so for several minutes.
1.38. Ventricles, 32 per minute.
1.47. Heart ceases to beat 37 minutes after breathing ceased. Cavities dilated and filled with dark blood. Pupils dilated to maximum extent.
Lethal dose in this experiment, 0.12 gm. per kilogram.

V. Guinea-pig, weight 308 grams.
12.09 o'clock. 0.054 gm. mescalin hydrochlorate, in solution, hypodermically.
12.10. Tremor of body. Increased restlessness. Runs around.
12.11. Restlessness. Convulsion as in last experiment.
12.13. Convulsive movements continued. Pupils dilated.
12.14. Gasping on side.
12 16. Dead. At autopsy, later, pupils found dilated to maximum extent. Heart stopped in diastole, cavities filled with dark blood.
Lethal dose in this experiment, 0.17 gm. per kilogram.

Experiments with mescalin hydrochlorate upon kittens gave practically the same results. The pupil was dilated even by small doses. The breathing became very rapid and shallow. Convulsions were produced similar to the ones reported in the above experiments, and the heart continued to beat after respiration had ceased. The lethal dose was found to be practically the same. The most important difference in effect was that in kittens the drug seemed to act from the very first to depress the muscular system, the animal resting throughout the experiment upon the belly, the extremities extended flat upon the table. They attempted to move around, but could not.

It is evident from these experiments that the effects of mescalin are widely different from those of anhalonin. It is much more powerful. The minimum lethal dose of mescalin in our experiments was found to be 0.12 per kilogram, whereas Lewin found the lethal dose of anhalonin to be 0.16–0.20.

While both alkaloids, in large doses, produce convulsions, those of mescalin are different in character from those produced by anhalonin. As already stated, the convulsions of anhalonin somewhat resemble those occurring in strychnine-poisoning. They are accompanied by some increase in the reflex excitability, and more or less opisthotonos, and they can be brought on by external stimulation. While the animal under the influence of mescalin exhibits, at times, great restlessness, nevertheless the effects are not accompanied by increased *reflex* excitability, and the animal appears rather less responsive to external stimulation than normally, and convulsions cannot be precipitated by such stimulation. Opisthotonos also is not a marked feature of the full effects of the alkaloid, although it is present to a slight degree during the convulsions.

It would appear that the convulsions produced by mescalin more closely resemble those caused by non-oxygenation of the blood. The effects of the alkaloid are accompanied by rapid and difficult breathing and symptoms of respiratory embarrassment. In Experiment III. this was true to such an extent that all the muscles of the body seemed to be brought into play to aid the animal in obtaining sufficient air, and the appearance presented was that of intense dyspnœa. Death also is preceded by respiratory failure—the heart continuing to beat for a variable length of time after the breathing ceases. After death the ventricles are found dilated and filled with very dark blood. Furthermore, Heffter,[1] who made a limited number of experiments with this alkaloid upon frogs, makes no mention of convulsions as an effect of the drug in that class of animals; whereas, in our experiments upon animals of higher development, convulsions were a constant symptom when the drug was administered in large dose. This alone would lead us to think that the convulsions produced by mescalin are asphyxial in character, and produced by the contact of the non-oxygenated blood with the motor nerve-centres, it being a well-known fact that asphyxial convulsions do not occur in frogs, whereas they do occur in animals of higher development. Brunton[2] states that if any drug produces convulsions in the higher animals and not in frogs, the probability is that the convulsions it produces are asphyxial and not due to a direct irritant effect of the drug upon the

[1] Heffter: Archiv f. exper. Path. u. Phar., 1894, 34, 65.
[2] Pharmacology, Therapeutics, and Materia Medica, pp. 189 and 237.

motor centres. This, taken in connection with the facts already stated, leads us to believe that the convulsions produced by mescalin are asphyxial in character.

From these experiments it is evident that mescalin has no influence upon the heart as a depressant even when administered in fatal doses.

When given hypodermically it dilates the pupil. No effect upon the pupil was obtained from dropping a five or a ten per cent. solution of the hydrochlorate into the eye.

The alkaloid appears to depress the muscular system and respiration.

In its constitutional effects mescalin much resembles cocaine, and the similarity in action will at once become apparent in comparison with the effects of the latter drug upon the lower animals.[1]

From the mother liquor left after the separation of anhalonin and mescalin, Mr. Ewell has succeeded in obtaining a *third alkaloid* entirely different in its chemical and physiological properties from the two already considered. The hydrochlorate of this third alkaloid, which was the salt used in our experiments, is white or of a slightly yellowish color. It forms nodular groups of radiating needle-like crystals (Fig. 4), which are readily soluble in water and alcohol. The taste of the crystals is slightly bitter and acrid, with a persistent after-taste. Its reaction is neutral.

We have performed a series of experiments upon the lower animals to determine as far as possible the physiological effects of this alkaloid.

I. Rabbit, weight 985 grams.

11.55 o'clock. 0.0133 gm. hydrochlorate of alkaloid 3, in solution, hypodermically.

11.56. Restless. Great tremor. Animal rises upon extremities, which are perfectly rigid and pointing outward from body, like the legs of a "sawhorse," and seemed to be propelled slowly around table by violence of tremor.

11.57. Quiet, on belly, hind legs flat on table. On touch extremities became rigid and violent tremor appears.

11.58. On feet, with rigid extremities and tremor, as above.

11.59. Quiet if not touched. Breathing rapid. On touch convulsive movements.

12.02. Breathing very rapid. Heart 156 per minute.

12.05. Breathing same. No convulsive movements on touch. Hind extremities flat on table.

[1] See H. C. Wood: Therapeutics.

12.07. Hops fairly normally, but uses back legs awkwardly. Recovery from this time, breathing and heart gradually becoming slower to normal.

Amount injected in this experiment, 0.0136 per kilogram of body-weight.

II. Rabbit, weight 512 grams.

12.07½. 0.01 hydrochlorate of alkaloid 3, in solution, hypodermically.

12.08. Tremor, especially of hind extremities.

12.09. Violent tremor. When hops, hind legs somewhat stiff.

12.10. Breathing rapid.

12.10½. "Saw-horse" phenomenon as in last experiment, lasting about 10 seconds, after which animal fell on side in tetanic convulsion. All muscles rigidly contracted. Opisthotonos and extension of extremities. Followed by gradual relaxation of all muscles.

12.11. Muscles flaccid. Breathing ceased.

Lethal dose in this experiment, 0.02 gm. per kilogram.

III. Rabbit, weight 1165 grams.

12.19½. 0.03 gm. hydrochlorate of alkaloid 3, in solution, hypodermically.

12.21. Tremor of body.

12.21½. Tremor so violent as almost to amount to convulsive movements.

12.22. "Saw-horse" phenomenon as in preceding experiments, after which animal fell on side. Convulsive movements. Rigid extremities. Opisthotonos.

12.22½. Gradual relaxation. Breathing found to have ceased.

12.35. Thorax opened. Heart still breathing. Heart ceased in diastole 27 minutes after breathing stopped.

Lethal dose in this experiment, 0.025 per kilogram.

IV. Rabbit, weight 476 grams.

11.37. 0.025 gm. hydrochlorate of alkaloid 3, in solution, hypodermically.

11.38. Violent tremor. Jumped up and fell on side in convulsion. Opisthotonos. Extremities extended and all muscles rigid. No movement.

11.39. Convulsive twitchings. Gradual relaxation.

11.40. Breathing ceased.

11.45. Thorax opened. Heart beating rhythmically, 21 per minute.

11.50. Heart beating more slowly. Finally stopped in diastole.

Lethal dose in this experiment, 0.053 per kilogram.

In guinea-pigs the alkaloid produced effects very similar to those produced in rabbits.

V. Guinea-pig, weight 708 grams.

12.29. 0.007 gm. hydrochlorate of alkaloid 3, in solution, hypodermically.

12.31. Slight tremor of ears.

12.34. Much startled by sudden noise, as rapping table with pencil.

12.41. Same. Restless.

12.47. Quiet. Jumps clear from table when blown upon, or upon sharp noise.

12.51. Same. Cries upon being touched. Runs awkwardly with violent tremor.

12.53. Increased reflex excitability continues. Not frightened by object brought rapidly toward it. Condition remained as described until 1.09, when gradually became normal.

Amount injected in this experiment, 0.01 per kilogram.

VI. Guinea-pig, weight 713 grams.

11.45. 0.0196 gm. hydrochlorate of alkaloid 3, in solution, hypodermically.

11.46½. Slight tremor. Runs around.

11.48. Violent tremor, especially on moving.

11.50. Violent tremor. Falls on side. Muscles of body and extremities contracted and rigid. Extremities extended. Opisthotonos.

11.56. Gradual relaxation. Hair on forepart of body "on end."

11.51 to 11.55. Alternating tetanic spasms and relaxation. Breathing absent during spasm, slightly accelerated between paroxysms.

11.56. Animal on side. Constant spasmodic twitchings of muscles of head, body, and extremities, continuing until 12.05. Heart and breathing rapid. Tetanic spasms can be precipitated by touch or irritation.

12 05½. Tetanic convulsion followed by relaxation.

12.06. Gasping. Breathing gradually becomes regular and slower.

12.09. Hair still "on end." Can stand on feet.

12.11. Moves around awkwardly. Recovery.

Amount injected in this experiment, 0.0275 per kilogram.

VII. Guinea-pig, weight 608 grams.

12.00. 0.0182 gm. hydrochlorate of alkaloid 3, in solution, hypodermically.

12.02. Tremor on moving.

12.04. Tetanic convulsion. Muscles rigid. Extremities extended. Opisthotonos. Followed by relaxation. Hair on forepart of body "on end."

12.05 to 12.10. Alternating tetanic spasms and relaxation.

12.10. Gasping. Opisthotonos.

12.12. Tremor. Spasmodic twitching.

12.14. Same.

12.20. Heart rapid. Breathing fairly normal.

12.26. Tetanic convulsion brought on by touch. Followed by gradual relaxation. Breathing found to have ceased.

12.30. Thorax opened. Heart still beating.

12.50. Heart ceases.

Lethal dose in this experiment, 0.03 per kilogram.

In frogs effects were produced which even more clearly indicate the physiological action of the alkaloid under consideration. These effects were similar to those occurring in guinea-pigs and rabbits. A series of experiments upon frogs was made, of which the following may be considered typical:

VIII. Frog, weight 183 grams.

2.33. 0.00549 gm. hydrochlorate of alkaloid 3, in solution, hypodermically (0.03 per kilogram).

2.37. Increased reflex excitability to touch.

2.39. Reflex excitability still more increased. Violent sudden extension of extremities on touch.

2.44. Tetanic convulsion upon touch or other slight irritation. Animal lies perfectly quiet; when touched, however, tetanic convulsion appears, with contraction and rigidity of all muscles, and extension of extremities, which lasts for a few seconds, followed by relaxation and quiet until again irritated.

Condition remained same for several hours, and was dead upon following morning.

IX. Frog, weight 268 grams.

12.02. 0.008 gm. hydrochlorate alkaloid 3, in solution, hypodermically (0.03 per kilogram).

12.06. Increased reflex to touch.

12.08. Reflex increased. Irritation produces violent sudden extension of extremities.

12.11. Animal lies perfectly quiet unless touched, when violent tetanic convulsion occurs, as in last experiment.

1.05. Spinal cord divided at about its middle. Reflex tetanic contractions persist below as well as above point of section.

Other experiments upon frogs were done with the same results.

From these experiments it is evident that the alkaloid is much more powerful than either anhalonin or mescalin, and differs from them also in its physiological effects. Its lethal dose in frogs, rabbits, and guinea-pigs is 0.02 to 0.03 gm. per kilogram of body-weight. The most marked effect of the alkaloid is to increase the reflex excitability of the animal. This was produced by doses as small as 0.0136 per kilogram. As the amount given was increased, this effect became more marked, and when large doses were administered violent reflex tetanic convulsions were produced. As with strychnine, these effects were due to action through the spinal cord, for they persisted below the point of section after the cord had been divided and the parts severed from connection with the brain. The similarity in action between this alkaloid and strychnine is remarkable. Experiments were performed in which a frog was given alkoloid 3, and another at the same time strychnine, and the effects of the two drugs were compared. Almost no difference in effect whatever could be distinguished,

the third alkaloid producing increased reflex excitability as surely and to as marked an extent as the strychnine.

The effect of chloral hydrate upon an animal to which the alkaloid had been administered is also of interest. To ascertain this, a lethal dose of alkaloid 3 was given to one frog, and to another the same dose of alkaloid 3, and in addition chloral hydrate in varying quantity in different experiments.

X. 3.40 o'clock. Frog A. 0.03 per kilogram hydrochlorate of alkaloid 3, hypodermically.

Frog B. Same, and in addition chloral hydrate, 1.00 per kilogram, hypodermically.

In frog A, increased reflex excitability was noted in four minutes. The effect deepened into reflex convulsions upon irritation, as in the experiments already reported, which continued until the death of the animal.

Frog B appeared normal at 3.45 and 4.00 o'clock.

4.05. Extremities appear weak, and animal rests upon belly. By no stimulation can any increased reflex excitability be demonstrated.

4.07. Same. Stupid. No increased reflex. Condition remained the same until death, at 4.20, apparently from effects of chloral. At no time did any increase in reflex excitability appear.

Other similar experiments were made in which the dose of the third alkaloid remaining the same (0.03 per kilogram), the amount of chloral administered was progressively lowered. It was found that no increase in reflex excitability appeared until the amount of chloral was lowered nearly to 0.25 per kilogram. As the amount was still further lowered, reflex tetanic convulsions and the typical effects of the alkaloid appeared. Furthermore, chloral appeared to act in frogs as a direct antidote in poisoning by the drug.

XI. Frog, weight 344 grams.

11.30 o'clock. Injected lethal dose of hydrochlorate of alkaloid 3, 0.0103 (0.03 per kilogram); also, 0.086 of chloral hydrate (0.25 per kilogram).

11.37. Slight increase of reflex excitability to touch.

11.48. Same, more marked. Extension of legs on touch. Stands normally.

11.53. Tetanic convulsions on touch. Stupid. Rests on belly. Tries to hop occasionally. Draws legs up normally. Condition remained same for several hours, and recovery upon following morning was complete.

XII. In this experiment the same lethal dose, 0.03 per kilogram, was injected, and but 0.125 per kilogram of chloral. Animal recovered.

In these experiments the amount of chloral given was insufficient entirely to counteract the effect of the alkaloid, but the animals recovered from what would otherwise have been a fatal dose.

From the results of these experiments we conclude that the most marked physiological effect of the third alkaloid is the production of increased reflex excitability, and, if the amount given be sufficiently large, reflex tetanic convulsions; this effect is produced by action through the spinal cord; chloral hydrate directly antagonizes this effect of the alkaloid, in small doses modifying the increase in reflex excitability, and in sufficiently large doses counteracting it entirely; and that the symptoms produced by the alkaloid in frogs, guinea-pigs, and rabbits appear to be identical with those produced by strychnine.

The action of the alkaloid upon the respiration and heart appeared to be entirely secondary to its effect upon the muscular system and the degree of involvement of the muscles of respiration. The breathing was absent during the tetanic convulsions, and more rapid than normal during the interval of quiet, as was also the heart.

No marked effect upon the pupil was found.

Other Constituents. In addition to alkaloids, mescal buttons contain other ingredients, the most important of which is a resinous substance, which may be found to play an important part as the active principle of the drug. It is soluble in alcohol and ether, insoluble in water, and seems to be of a complex nature, as it can be separated into two or more portions by proper solvents. The buttons also contain other substances which possess more of chemical than of pharmacological interest. These include one or more wax-like bodies, and some of the carbohydrate constituents of the plant.

Therapeutic Uses. The conditions in which it seems probable that the use of mescal buttons will produce beneficial results are the following: in general "nervousness," nervous headache, nervous irritative cough, abdominal pain due to colic or griping of the intestine, hysterical manifestations, and in other similar affections where an antispasmodic is indicated; as a cerebral stimulant in neurasthenia and in depressed conditions of the mind—hypochondriasis, melancholia, and allied conditions; as a substitute for opium and chloral in conditions of great nervous irritability or restlessness, active delirium and mania, and in insomnia caused by pain. In the last condition it

acts to produce sleep, not as a hypnotic, but by relieving the cause of the insomnia. In full physiological doses it produces insomnia, but in therapeutic doses it does not have this effect.

The following cases in which the drug was used may be mentioned briefly:

I. Gentleman, aged fifty-five years, Chronic bronchitis with asthmatic attacks; much distressed by an irritative cough, which kept him from sleeping. A piece of the centre of a button the size of a pea was administered in the afternoon, to be dissolved slowly in the mouth. The irritative cough was speedily relieved. He took a second similar dose at bedtime, and slept well through the night, which he had not done before for a long time. He returned to his home in New York, and kept up the use of the drug with continued relief. In a letter received from him recently he states that he has improved very much, being able to sleep all night without rising, which he had not been able to do for two years; and that, although he has no need to use it upon some days, he carries a piece of a button in his pocket constantly, as it relieves the tickling in his throat at once and gives greater relief than any other remedy which he has ever used. It appears to have no curative effect—merely relieves the irritative cough.

II. Gentleman; Principal of High School; aged twenty-five years. Neurasthenia of six months' standing. The effect of the drug in this case seemed little less than marvellous. Three buttons were administered within an hour. This was followed by the characteristic color-visions of the drug, and relief from the bodily and mental fatigue with which he had suffered for six months, and he declared that he was "himself again, cheerful and happy." On the next day and for several days thereafter he continued to feel the beneficial effects of the drug. He has continued its use in doses of one-half a button when he feels it to be necessary. It invariably relieves the sense of bodily and mental fatigue.

III. Lady, aged thirty-three years. Nervous prostration. The drug was administered in this case as in the last, but in smaller doses, with a marked beneficial effect. Mental and physical exhaustion relieved, and power of work increased to a marked degree. No reaction.

IV. Lady, aged forty-nine years. Chronic phthisis with facial neuralgia, and catarrh of pharynx, larynx, and bronchi. The fluid-extract of anhalonium was administered with beneficial effect. The irritative cough was relieved to a marked extent, the spells of coughing being less frequent, and less violent and prolonged. Although she has been taking the drug but a comparatively short time, she has suffered much less than formerly from the facial neuralgia.

The following cases were reported by a gentleman of a Western State. The drug was administered under the supervision of his family physician:

V. Gentleman, aged fifty-six years; large and strong physically. "Softening of the brain;" onset dating back about a year. Under the care of his two brothers, who were physicians in Kansas. Was at times violent and required the constant attendance of a physician and two attendants. In an attack of violence, opium, in the form of laudanum, and morphine were given, commencing on Thursday, until the following Sunday, without beneficial effect. Upon Sunday, at 2 P.M., he was given a teaspoonful of tincture of anhalonium. A teaspoonful was also given every half-hour from 6 until 9 P.M. At 10.30 the patient went to sleep, and awoke at 7 o'clock, Monday, in rational condition. Felt so much improved that he left the next morning for his home in Texas. The course of the original disease was not influenced by the drug and he died a few months later.

VI. Sister of the above-mentioned gentleman reporting cases. "Very low and out of her head." One of the physicians above referred to used chloral to quiet her, and, this failing, administered tincture of anhalonium. It quieted her in a few minutes, and she slept well and long. It seemed to be the turning-point in her illness, as she fully recovered.

The same gentleman reports that his wife formerly used to take the tincture for nervous headaches, and that it always relieved her. She has them so seldom now that she does not use it.

The following preparations are suggested:

Extractum Anhalonii Fluidum (100 per cent.). Dose, 0.50–1.00 gm. (ten to fifteen drops).

Tinctura Anhalonii (10 per cent.). Dose, 4.00–8.00 gm. (one to two teaspoonfuls).

Anhalonium (in form of buttons or powder). Dose, 0.50–1.00 gm. (seven to fifteen grains).

The tincture should be made by the process prescribed in the *U. S. Pharmacopœia* for the preparation of tinctures. It should be of 10 per cent. strength. The fluid-extract should be made 100 per cent. strength, and in accordance with the method prescribed in the *U. S. Pharmacopœia* for the preparation of fluid-extracts.

The taste of these liquid preparations is very bitter, but may be disguised by a suitable vehicle, such as a mixture of fluid-extract of licorice and elixir of yerba santa.

In conclusion, we would say that Anhalonium Lewinii (mescal buttons) must not be confounded with the intoxicating drink "mescal," used by the Mexicans and others. This drink is the fermented juice of one or more of the species of *Agave*.

FIG. 1.

FIG. 2.

a b c

FIG. 3.

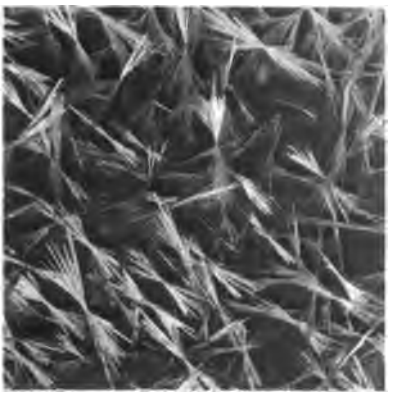
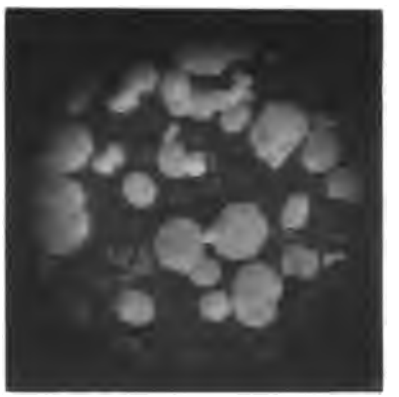


FIG. 4.



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Explanation of the Plate.

Fig. 1. Anhalonium Lewinii—growing plant. Shows top which, when cut off and dried, is known as mescal button.

Fig. 2. Mescal button.
- *a.* Under surface.
- *b.* Eye view.
- *c.* Upper surface.

Fig. 3. Anhalonin hydrochlorate crystals.

Fig. 4. Groups of crystals of the third alkaloid.

A CASE OF LEUCÆMIA.

By J. H. MUSSER, M.D.,
AND
JOSEPH SAILER, M.D.,
OF PHILADELPHIA.

E T. L. (Case Series K, No. 61, 1895), aged thirty-one years; male; laborer; admitted to the Presbyterian Hospital May 30, 1895.

Family history: Father and mother both died of alcoholism; two sisters living and well. Family history otherwise unknown.

Previous history: The patient has had the usual diseases of childhood. He worked on a farm since he was seven years old. He had malaria fifteen years ago; typhoid fever four years ago, followed by dropsy of the legs. Soon after recovery he contracted gonorrhœa.

History of present disease. March, 1895, the patient had a severe attack of influenza, when he suffered from severe pain in the loins and legs. The pains persisted, and in May of the same year he applied to the hospital for treatment of the pain, and on account of a movable tumor which he accidentally discovered in his left side, and which gave him pain when reclining on that side. When questioned he stated he was weaker than usual, and that he had lost some flesh and had irregular abdominal pains.

Condition on admission: Patient was a white man, of moderate height, and weighed one hundred and sixty pounds. The skin and mucous membranes were of good color. The countenance was bright. The pupils were normal, and reacted to light and distance.

The chest was well formed. The respiratory movements were shallow and rapid, but nothing abnormal was found on physical examination. The apex-beat of the heart was in normal position. A soft systolic murmur not transmitted was heard at the apex and at the aortic cartilage. The cardiac dulness was not increased. The pulse was slow, of fair strength and volume. The artery wall showed slight evidence of endarteritis.

The abdomen was distended, and on palpation a tumor could be distinctly outlined occupying the position of an enlarged spleen. The lower edge was painful; the right border extended to the median line, and the lower border to within an inch of the ilium. The splenic dulness extended from the eighth rib to the transverse umbilical line, and in the anterior axillary line

was twelve inches in length. Dulness extended from the xyphoid cartilage to the left eight inches in a direct line, and from the umbilicus to the lumbar muscles. The upper limit of liver-dulness was normal; the lower border extended one inch below the costal margin; the edge could be felt. The abdomen measured thirty-four inches at the umbilicus.

With the exception of the afore-mentioned weakness and the hurried breathing there were no other subjective symptoms. The appetite was good, the bowels regular, and there was no indigestion. The urine contained no albumin or sugar, nor abnormal elements under microscopical examination.

June 11, 1895, the abdomen measures thirty-three inches, and the length of the spleen is ten inches. The edges can easily be palpated. The left leg has been swollen and tender during the past week. The blood-examination shows hæmoglobin 34 per cent., red blood-corpuscles 4,000,000, white blood-corpuscles 57,2000.

The patient remained in the hospital until the 10th of August. He gained in strength to a remarkable degree. The abdomen was reduced to thirty-one inches in circumference, but the spleen remained about the same. During July the inguinal glands became enlarged and painful, and during both June and July the left leg was more or less œdematous, and the seat of pain. When the patient was discharged the white blood-corpuscles numbered 300,000; the red blood-corpuscles 4,100,000. Notwithstanding the increase in strength the patient lost ten pounds in weight. His temperature was normal, the pulse ranged between 80 and 90, and the respirations 20 and 26 per minute.

Readmitted December 25, 1895, suffering from the symptoms enumerated above, although greatly intensified, particularly the pain in the left hip and abdomen. Both legs are œdematous and there is œdema of the trunk in moderate degree. The patient is not as strong, but has not lost much flesh.

On physical examination the face and hands are observed to be reddened, and there is a marked flush on each cheek. The remainder of the body is pale and waxy as in anasarca. The radial arteries are extremely atheromatous. This change and the occurrence of anasarca are the most marked objective signs. The systolic murmur at the apex is more pronounced, and is transmitted into the axilla. The upper limit of liver-dulness is normal, but extends an inch below the costal margin, where it is palpable. The spleen is larger than on the previous examination. The epigastric region is dull on percussion due to the enlarged left lobe of the liver and the encroachment of the spleen. There is a large amount of ascites. The hæmoglobin is 30 per cent.; red blood-corpuscles 3,000,000; white, 640,000.

The patient died on the 7th of February. During the month of January the anasarca became extreme. The temperature ranged from $96\frac{2}{5}°$ to $99\frac{1}{5}°$, the pulse between 84 and 120, and the respirations 24. There were several attacks of epistaxis. From the day of the last admission there was painless diarrhœa, with stools containing mucus and occasionally blood. Death took place suddenly. He awakened from sleep with a sharp cry, and was imme-

diately afterward found semi-conscious. Frothy blood and mucus were discharged from the mouth, and death took place in a few moments.

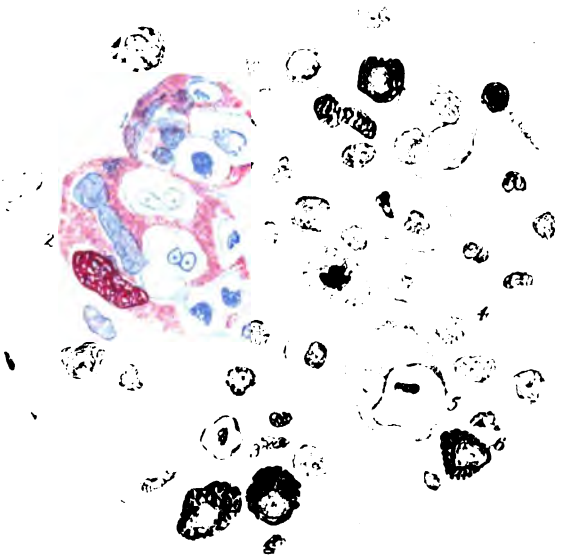
Autopsy. A portion of the body only could be examined. The tissues in the abdominal cavity were nearly filled with serum. The pleural cavities were about one-fourth full of fluid, and the pericardium contained six ounces. The heart was flabby, the muscle pale, the left ventricle half an inch thick. The right ventricle contained a light-green clot. A small green clot was seen on the mitral valve. The aortic valves were thickened, and there were spots of atheroma on the aorta.

The left lung was œdematous, and the lower part collapsed. The right lung was in the same condition. At the apex evidences of old tubercle were seen. The large bronchi were filled with bloody froth. The lymphatic glands in the mediastinum and the roots of the lungs were enlarged, gray, and succulent. The spleen was ten and a half inches in length; weight 990 grammes. It was firm, chocolate colored, and mottled with fine dark spots. Malpighian bodies not prominent. Liver, weight 3320 grammes; greatest breadth fourteen and a half inches. On close inspection fine irregular streaks were seen running throughout on section. Thyroid gland apparently normal. Pancreas normal; nothing unusual in the appearance of the stomach. In the large intestine throughout its whole extent there were many large serpiginous ulcers. In the lower portion of the ileum there were four irregular punched-out ulcers. The rectum was the seat of ulceration. The upper part of the small intestine was injected in spots, but there were no hemorrhages or petechiæ. All of the abdominal glands were enlarged, especially those about the gastro-hepatic omentum. They were of a light-greenish tinge, and very succulent. The spinal cord was removed for examination. Brain not examined.

The Blood. The blood of the patient was examined on the 30th of January of this year and found to contain 1,571,875 erythrocytes and 382,188 leucocytes per cubic millimetre, or a proportion of one white to four red cells.

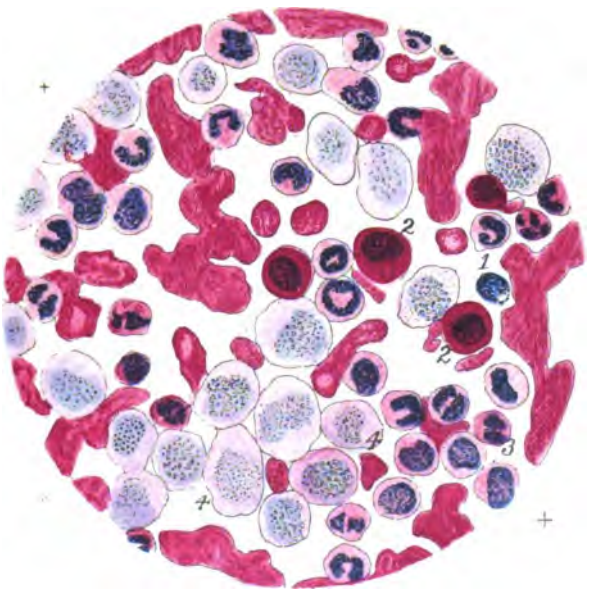
In order to determine the specific gravity, a picnometer holding about 6 grammes was filled with blood taken from the median vein of the forearm; the result was 1049.88; and as the percentage of error of this method is very slight, the result may be taken as fairly accurate.

Chemical examination. The blood from the picnometer was then boiled for about twelve hours in the presence of a great excess of ammonium sulphate, filtered, and the filtrate examined by the usual method for *peptone*. The characteristic reaction occurred, but as a recent thorough investigation of this method by Dr. Caspar Miller has led him to believe that it does not positively exclude the albuminoses, we cannot assert that peptone was certainly present. Certain other compounds, however, that have been described in leucæmic blood—that is, xanthin, hypoxanthin, lactic and acetic acids, and acetone—were absent from the specimen examined. The determination of the degree of alkalinity and of the proportion of the fibrin-forming elements could not, unfortunately, be made. The former because of the lack of appa-



Lymph-gland, retroperitoneal region. Hardened in alcohol; Rosin's stain. × 1500.

1. Globiferous cell. 2. Globiferous cell containing polynuclear and eosinophile cells. 3. Polynuclear cell. 4. Mononuclear cell. 5. Globiferous cell 6. Eosinophile cell.



Blood-leucaemia. Hæmatoxylin and eosin.

1. Lymphocyte. 2. Eosinophile cell (mononuclear). 3. Polynuclear leucocyte. 4. Large mononuclear leucocyte (myelocyte?).

ratus at the hospital, the latter because the withdrawal of the considerable amount of blood required by the Bleibtreu method, about 100 c.c., was considered unjustifiable in the serious state of the patient.

Microscopical examination. A number of cover-glass preparations were made and fixed, either by heat, or the ether-alcohol mixture. The latter were stained in the usual way with hæmatoxylin and eosin. The most characteristic feature of the blood so prepared was the presence of a large number of leucocytes from two to three times the size of a red cell, containing a single round nucleus, either eccentrically placed, or, less commonly, in the centre. This nucleus usually took the stain poorly, appearing as a pale blue disc, while the protoplasm of the cell had a faint purplish tinge. There were also a number of mononuclear cells, slightly smaller on the average than the first-mentioned group, whose nuclei stained deeply, quite as well as those of the polynuclear cells. Very often these nuclei were irregular and belonged to the transitional type, but as every gradation existed, it was thought best not to attempt to separate them. A third form consisted of large irregular cells with large nuclei, staining very poorly, and a colorless protoplasm without a very distinct boundary, that appeared to be granular. These cells were three or four times larger in diameter than the red blood-cells. The proportion of all these mononuclear elements to the whole number of leucocytes was 66.2 per cent. As nearly as could be determined, 10 per cent. of all the mononuclear elements belonged to the last type described.

Another group of mononuclear cells was the ordinary lymphocytes with the small deeply staining nucleus and the narrow rim of protoplasm; of these there were but 0.8 per cent. The ordinary polynuclear elements of the blood formed 24.4 per cent. of the total number of leucocytes. The eosinophil cells could be divided into three groups, the mononuclear and polynuclear forms, with deeply staining nuclei and coarse, closely packed granula, and certain mononuclear cells, with large pale nuclei and rather finer, more scattered granula. Sometimes these granula were dispersed as if the cell had burst during the smearing. In each group of fields containing 1000 leucocytes, 19.8 nucleated red blood-cells were found, a proportion to the whole number of erythrocytes of about 0.47 per cent. It now remained to determine the proportion of mononuclear cells containing neutrophilic granula. The preparations fixed by heat, for some unknown reason, for other preparations fixed at the same time and in the same manner were excellent, refused to stain well by the ordinary aniline mixtures, such as Biondi's or Rosin's stains or the mixtures containing basic fuchsin. The best success was obtained with a mixture suggested by Dr. A. E. Taylor, containing methylen-blue, methyl-green, neutral red and orange. Counts made of preparations stained by this method showed that 62 per cent. of the mononuclear elements contained neutrophilic granula. These cells were composed largely of the smaller cells with dark nuclei, that varied from the round to the transitional type; but besides these, the neutrophilic granula were found in the large cells with the pale irregular nuclei. These latter

may be taken to correspond to the myelocytes of Ehrlich, for, although the absence of amœboid movement was not determined, they agreed in the other characteristics.

Differential count. To summarize the results, then, there were:

Erythrocytes	80 per cent.
Of these there were	
Nucleated	0.47 "
Leucocytes	20 "
Of these	
Mononuclear elements	66.2 "
Polynuclear elements	24.4 "
Eosinophil cells	8.6 "
Lymphocytes	0.8 "

Microscopical examination of the tissues. When the patient died Dr. Hughes kindly provided pieces of the lung, liver, spleen, kidney, pancreas, lymph glands, and a small section of the radius. The study of these specimens is not yet complete, as some of the methods of fixing and hardening require more time than has been at our disposal, and, very unfortunately, a piece of the bone that was rapidly decalcified was spoiled in the process, so that as far as the bone-marrow is concerned, perhaps the most important of all, it can only be said that no peculiar changes can be detected. It contains considerable fat and cells of various sizes, some of them containing the oxyphil granula. The lymph glands were not especially enlarged, one from the bronchial region contained considerable black pigment. In all were found numerous cells with oxyphil granula. A peculiar feature was the presence of enormous polynuclear cells. One of the larger of these measured not less than 31½ by 35 microms. In the substance of these cells were found broken-down red blood-cells, some pigment, and apparently leucocytes. They contained a number of nuclei, relatively small and scattered; the outline was fairly regular. They showed particularly well in sections stained with Rosin's mixture, the nuclei appearing a bright green and the protoplasm taking a faint reddish tinge.

In appearance these cells strongly suggest the giant-cell of sarcoma. But it is to be observed that they correspond very closely to the description of the globiferous cell described by Biondi in Ziegler's *Beitrage*, Band xviii., Heft 1. Moreover, the presence of degenerated cells in the midst of the protoplasm marks them as unquestionably phagocytic in their nature, and although Biondi's article is unfortunately not illustrated, it seems reasonable to conclude that these cells are the same as those found by him in his experimental work with toluylendiamin. It is perhaps permissible to draw the inference that, if active cell-destruction is taking place in the lymph glands, the fact is

favorable to the theory that they are not the primary seat of the disease. A further proof of this cellular disintegration is to be found in the preparations stained by Quincke's method for iron, in which numerous cells are found that stand out sharply from the general background.

The spleen shows increase of the lymphoid elements, and a certain amount of hyperplasia of the connective tissue. As in the glands, the number of oxyphil cells appears to be large, and there are in addition certain large cells with one or more small nuclei and a protoplasm that has a strong affinity for the acid stain; but, unlike the eosinophil cells, stains with a uniform color. One of these cells measured 17½ by 42 microms. The reaction of the protoplasm shows that they are probably degenerating, and perhaps they represent a late stage of the globiferous cells. It appears, therefore, that in this tissue, also, cellular destruction is taking place. Many of the cells, as in the glands, contained distinct traces of iron.

The parenchymatous elements of the pancreas exhibited considerable degenerative changes; the nuclei stained poorly and the cells were swollen and irregular; there was also a considerable excess of connective tissue.

The eosinophile cells found in the tissues fixed by picric acid and stained with Gollasch's mixture showed beautiful chromatine figures, and in many of them the nuclei contained nucleoli, none were found with karyokinetic figures.

The other organs showed characteristic leucæmic infiltration: the liver was slightly fatty; the kidney showed here and there a partial obliteration of the space between the glomerulus and its capsule, but was, on the whole, in excellent condition. The lungs presented a peculiar feature. The alveoli were filled with a substance that appeared to be homogeneous, stained deeply with the acid stains, and was partially adherent to the epithelium. It could not be celloidin, for that takes the basic aniline colors, and probably represents a coagulated exudate, but its exact nature we have not determined.

The symptoms and course of the disease were not unusual. With the exception of moderate enlargement of the lymphatic glands of the groin during life these structures did not appear to be involved, and were excluded as pathological factors in the leucæmia. From the physical examination and the results of the examination of the blood during life, we considered the leucæmia was of myelogenic and splenic origin. The histological findings appear to show the bone-marrow was not affected, while the lymphatic glands had undergone the changes peculiar to leucæmia, and that the disease was, contrary to our belief, of the splenic and lymphatic variety. It seems, therefore, that the blood examination does not suffice to distinguish the types.

The case was one of lymphatic and splenic leucæmia notwithstanding the blood did not indicate that the lymphatic glands were affected during life.

In the histological study of the tissues attention is called, first, to the globiferous or giant-cell in the lymphatics, which are undoubtedly phagocytic. Second, to the iron found in the tissues, showing that blood-destruction must have been in progress. Both conditions point to an infectious process. The occurrence of the extensive intestinal ulceration not leucæmic, with the histological findings, seems to indicate that a process somewhat allied to that in pernicious anæmia was present, either from the beginning of the disease or set in, the result of a terminal infection.

SUMMARY.

Clinical. Weakness, lumbar pain, and the accidental discovery of a tumor in a male aged thirty-four years. Enlargement of the spleen, anæmia and leucocytosis, enlarged inguinal glands, great anasarca, occasional epistaxis, colitis. Blood showed evidence of disease of bone-marrow.

Anatomical. The internal organs showed changes seen in leucæmia. *Iron* in the tissues. Phagocytes or globiferous cells in the glands. A further report will be made on the histological structure of the spinal cord. The urine should have been submitted to a quantitative examination.

DISCUSSION.

DR. WELCH: I have been recently interested in the study of sections of organs from a case of splenic-myelogenous leukæmia in which the blood-vessels of various organs, and particularly of the liver, contained in large number the large bone-marrow cells which are characterized by irregular budding nuclei. These cells, it is now known, may be swept into the circulation in various affections, other than leukæmia, and may be found in the pulmonary capillaries. The recent studies regarding emboli of parenchymatous cells have directed attention to the frequency of this occurrence. In the case of leukæmia referred to these bone-marrow cells constituted a considerable part of the cells found in the capillaries of the liver. From Dr. Musser's description I infer that the large multi-nucleated cells observed in the lymphatic glands were of a different character.

PROTRACTED SIMPLE CONTINUED FEVER.

By J. M. Da COSTA, M.D., LL.D.,
of Philadelphia.

I propose in this paper to examine into the history and clinical features of fevers of long duration that are not typhoid fever, and to ascertain in how far these continued fevers form a type of their own. Let me first describe, by way of introduction to the subject, a couple of cases of most unusual length: one, seen some years ago from the beginning to the end of the disease, and often since; the other, a more recent one, investigated repeatedly during its course.

Case I.—A number of years ago a young girl was brought to me with very poor digestion and great irritability of the stomach. By strict diet, the use of effervescing mixtures and laxatives, the disorder yielded in ten days, and free bilious discharges, for the most part dark-colored, took place at its end. Shortly afterward an inexplicable fever arose that lasted for three months. The fever was never very high; it did not, I think, ever exceed 103° F.; it was not ushered in by a chill, nor did chills happen during its continuance. There were, as in any fever, a morning remission and an evening exacerbation, but never to a marked degree; the fever was for weeks remarkably regular, only at times and at no stated periods, showing irregularities in its course, and its subsidence and disappearance were as gradual and unmarked by violent changes as its onset. Late in the disease some sweating happened.

Beyond the extraordinary fever there was nothing to note; there was no cerebral symptom, save occasional headache; neither nausea nor vomiting; no epistaxis; no diarrhœa, the bowels, indeed, were rather sluggish; no abnormal lung or heart condition; no albumin in the high-colored fever-urine; no eruption of any kind, not a single, even doubtful, rose-spot. A slight enlargement of the spleen was made out, but it was not decided. Indeed, there was nothing whatever amiss except the apparently interminable fever. The convalescence did not prove a protracted one; emaciation was obvious, yet, considering the length of the fever, not extreme; there was no falling out of the hair. I regret that I have no record of the state of the nails, and am not certain whether the ridges which Longstreth and I have so constantly found after typhoid fever, were present. Neither before, at the time, nor

since, has there been the least evidence of hysteria. Indeed, the girl of eleven years is now a young lady in the twenties, of unusual composure and vigor, though showing symptoms of gout, which she has inherited from her father. There was some talk of her having had malaria before the fever outbreak, but this was mere surmise, and the long fever was totally uninfluenced by quinine, as, in truth, it was by any other remedy. It seemed to leave when it had determined to leave.

CASE II.—A girl, fourteen years of age, was seen by me with Dr. Spivak in January, 1894, when she had been in bed with fever for over a month. When she came under his care she had been ill for two weeks, without abdominal symptoms, except a slight gastric disorder at the onset, but with decided fever; indeed, the temperature was 105° F., at or near which it stayed for three weeks longer. It then gradually declined, reaching 101° in the eleventh week, the fever not ceasing until at the end of the twelfth week, and disappearing gradually. At no time, save for a few days, was there more than one degree difference between the morning and evening temperatures. In these few days the temperature several times fell to 99°. Sometimes the fever was higher in the morning than in the evening. There were no catarrhal symptoms or bone-pains; dryness in the throat was complained of, yet nothing but injection was to be seen; the tongue was dry. Neither meteorism, nor diarrhœa, nor abdominal rose-spots, nor any other kind of eruption existed. The urine was simply a fever-urine. The patient took food well, and even enjoyed it. The spleen did not extend beyond the border of the ribs. There was restlessness, but no headache. The pulse was rapid, always compressible; there was no cardiac disorder. In the eighth week some bronchial symptoms were found, and at the middle of the right lung anteriorly a spot was detected over which the percussion-resonance was impaired, and the breathing, which had been about twenty, became more hurried, but all this passed away in two weeks, leaving still the steady continued fever.

Quinine in small doses, quinine in large doses, produced no effect, although much buzzing in the ears was complained of. Salol, as well as the ordinary coal-tar antipyretics, had but a temporary influence on the fever, as did cold sponging, and getting the patient out of bed. There appeared to be more effect from salol than from anything, except it was from the iodide of potassium. After a few days of this treatment the fever stopped. But it is a question whether it had not worn itself out. The convalescence was not protracted.

I saw the girl about three months after her recovery. She was in excellent health, with ruddy cheeks. All traces of the emaciation, which had never been very great, had gone, and she had not lost her hair.

When we take these two cases together we find an apparently causeless fever of extraordinary duration, and presenting, like idiopathic fevers, no definite lesions. The cases are alike in the continu-

ance of the fever, in the very gradual yielding, in the absence of marked remissions or of relapses; they are alike in some gastric symptoms which happened in the early part of the case, and then subsided, while the fever went on unchecked; they are alike, too, in the absence of any cerebral symptoms, except it be restlessness and occasional headache, and in the very slight, indeed doubtful, enlargement of the spleen.

I record these two cases as examples of the most protracted ones of simple continued fever I have encountered, but there are cases, much more numerous, in which the disease lasts from two to three weeks, with exactly the symptoms described, and, though much shorter than these long-drawn out instances, considerably longer than the simple continued fever ordinarily met with of about a week's duration. I have seen cases of this which it would be tedious to describe in detail, but I may mention that among the more pronounced were some among brokers and speculators in times of commercial panic, and that delirium in them was not an unusual symptom.

Let us contrast this fever-type, especially in instances of extraordinary length, with other fevers of protracted duration. To take, first, typhoid fever. Every instance of long-continued idiopathic fever is presumably typhoid fever. Yet typhoid fever does not last three months, unless kept up by complications, or unless repeated relapses happen. I have known a case prolonged for three months, in which temperatures of 105° F. repeatedly existed; but the enteric symptoms were throughout marked, and at the autopsy, besides the characteristic lesions in the ileum, an extensive colitis was found with thickening, and, here and there, sloughing of the mucous membrane of the large intestine, fully explaining the long fever and the frequent intestinal discharges. I have met with another instance of long-lasting typhoid fever with persistent high temperature, and similar intestinal affection, though in this case recovery took place. In both these cases there was no evidence of relapse, and the enteric signs were pronounced, making them totaly unlike the ones we have here detailed, and the eruption was very marked. This, in a very long case of typhoid fever, Murchison found to appear almost daily up to the sixtieth day.

Taking ordinary cases, the characteristic temperature-tracing, the crops of eruption, the nervous symptoms, the intestinal features, are

wholly unlike what we are here examining, and the definite cessation of the fever in the fourth week is one of the most certain phenomena. Nor is it necessary to do more than mention how great the dissimilarity to remittent fever, even if of more than average length, and to relapsing fever. Should a doubtful instance of the kind arise, the microscopical examination of the blood for the characteristic micro-organisms would speedily clear up the doubt. With reference to so-called typho-malarial fever, the history of the case and the enteric symptoms and enteric lesions are of great significance. More difficult will it be to distinguish the continued fever that may follow a remittent fever. But the different onset of the malady, the chills or chilly sensations at the beginning, the disturbance of the digestive organs, the irregularity of the temperature, a sign to which Gervais Robinson[1] has particularly called attention, are specially significant. Then, too, the malarial organisms are of the greatest aid. Councilman[2] found them in the blood in many examinations he made of this continued malarial fever. The organisms were rather large crescentic forms, free in the blood and not in the corpuscles.

I think the greatest resemblance to very long idiopathic simple continued fevers is furnished by the protracted fever we sometimes meet with during epidemics of influenza. Here the catarrhal symptoms may long have passed away, though the fever strangely persists for weeks, a coated tongue, anorexia, slight irritation in the lungs, a few scattered râles, and a point of less perfect expansion being, perhaps, all that is found. I saw, among many others, during the epidemic of influenza a few years since, a case of this kind with Dr. Darrach, who kindly sent me the temperature-record. The boy was ill with fever from June 5th to July 19th, and the fever, never very high, gradually left, but even after it had gone the temperature was occasionally above 98.4°. In the beginning the signs of influenza were marked and a few bronchial râles were heard. A brother, eight years of age, was similarly affected. The temperature was, with the exception of some morning temperatures, above normal from January 19th to March 5th, and even then the evening temperature registered at times 99.5°; the highest temperature attained was 103°. The epi-

[1] TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, 1888, vol. iii.
[2] Ibid., 1887, vol. ii. p. 229.

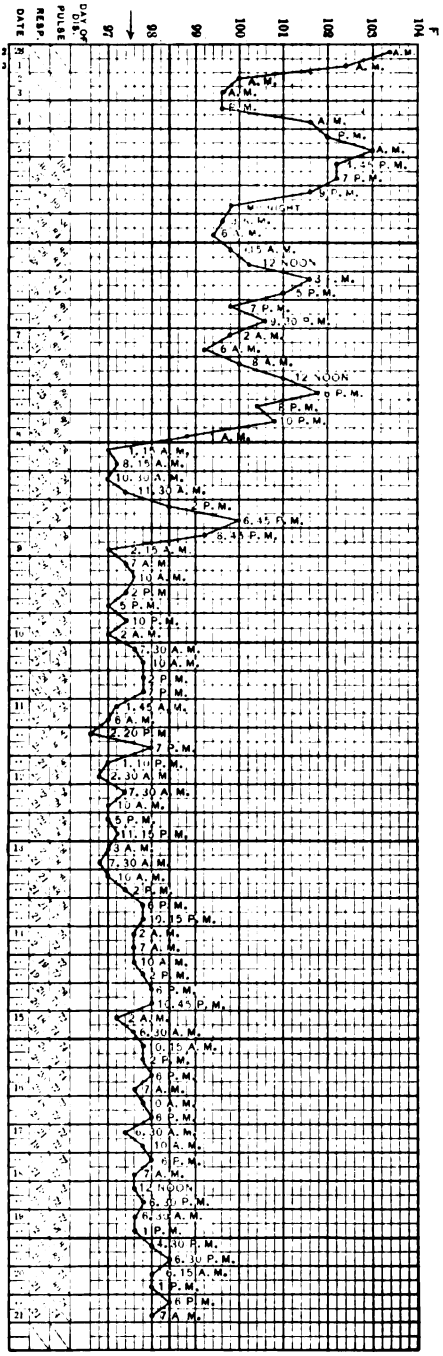
demic character of the cases and the bone-pains and other marked influenza-symptoms at the onset tell their true nature.

There is another form of influenza, one in which the catarrhal symptoms affect the stomach and intestines, that it may be difficult to distinguish from the cases of simple fever which are not of influenza-origin. I will cite a case seen a few years since, when epidemic influenza was raging, with Dr. De Young, who has given me the temperature-record he kept, which, as the study of pure instances of the enteric form of catarrhal fever or influenza is rare, especially with reference to temperature, I here reproduce:

CASE III.—The patient was a woman, sixty years of age. She was in perfect health when she was seized with shiverings, fever, bone-pains, and nausea. The tongue quickly became coated, the appetite was entirely destroyed, and vomiting occurred. The urine was high-colored and free from albumin. The bowels were constipated or irregular; there was no jaundice. No chest-symptoms whatever existed, or, indeed, were present at any part of the case, though the respiration was somewhat accelerated. There were great variations in temperature, and while, as a rule, the morning temperature was lowest, the reverse also was noticed.

The temperature sank to 97° F. on the eighth day of the disease, rose to 100° in the evening, fell again to 97° on the ninth day, and from that time on remained subnormal, often below 97°, to the nineteenth day, when it attained the normal. The prolonged subnormal temperature in the slow convalescence, as well as the great variations during the fever, the sudden onset with marked bone-pains, and the decided gastric symptoms, are very characteristic features of influenza, and, with the knowledge of the prevalence of an epidemic, distinguish its gastro-enteric form from the cases of simple continued fever under discussion.

I pass next to groups of cases which, whatever their origin, must be here considered, namely, cases of continued fever not typhoid, having a duration of several weeks, and found in particular localities, or due to special recognizable causes. The very existence of such cases has been denied. But let me say at once that, with full appreciation of the difficulty of their clear discernment; with the frankest acknowledgment that their study may baffle even the most sagacious physician; with knowledge gained by experience that anomalous typhoid fever will lurk and hide its features completely where it is unsuspected—I still believe in the existence of a continued fever of considerable duration that is not typhoid or a malarial fever that has become continuous.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But the most common form of simple continued fever, not merely ephemeral, but lasting at times for some weeks, is the fever of the tropics, especially as met with in the West Indies and parts of South America and of India. It is the ardent fever of the older writers; it is, in its more violent form, the inflammatory fever Copland describes as a variety of ardent fever. It has a duration of two weeks, does not occur in epidemics, and, notwithstanding the violent symptoms of intense headache, delirium, flushed face, and full pulse, ends generally in recovery. Death, however, may take place between the sixth and ninth days by coma. With this kind of fever, though differing in intensity, I class the continued thermic fever of Guitéras,[1] observed especially at Key West, and in which wakefulness, great nervous excitement, disordered muscular functions, and unimpaired appetite were common, but in which no eruption nor any of the special symptoms of typhoid fever, nor the characteristic ascending temperature-tracings of the first week were seen. The temperature was often as high on the first day as at any time. In two cases death occurred in the second week with hyperpyrexia. In some of these instances of prolonged fever, autopsies were made by Guitéras[2] and the lesions of typhoid fever were not found.

A variety of this continued fever is the one described by Murchison[3] as "Asthenic Simple Fever," a fever lasting two or three weeks, with rather feeble pulse, constipation, disturbed sleep, and increasing weakness. It often follows great mental or bodily fatigue, and is never fatal.

A continued fever of remarkable type, in which convulsions as well as chest-symptoms may arise, may be due to starvation. I have described such cases as "Starvation-fever."[4] An autopsy in two instances showed a normal condition of the intestinal glands.

There are other forms of simple fever met with in different localities which may here be inquired into, and which are traceable to special causes. The so-called "Malta Fever" or "Rock Fever," or the fever of the Red Sea ports is one, and, according to Milnes,[5]

[1] Therapeutic Gazette, March, 1885. Also, Report of the Sup. Surgeon-General Marine Hospital Service, 1884-85, Washington, 1885, 95-107.

[2] TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, 1887, vol. ii. p. 222.

[3] Treatise on Continued Fevers, p. 681.

[4] Transactions of the College of Physicians of Philadelphia, third series, vol. v.

[5] Lancet, June, 1892.

irregularity of temperature may continue for weeks or months, and rheumatism is not an uncommon complication. Another is the atypical Continued Fever described by Cain[1] at Nashville, and existing also in other parts of the United States, bearing no relation to typhoid fever, and thought to be dependent upon a septic agency arising from the soil. Descriptions of the Cyprus Fever[2] leave a doubt on the mind whether it is not a form of relapsing fever; and Baumgarten's[3] interesting paper on "A Simple Continued Fever" at St. Louis has not dispelled, chiefly owing to the character of the autopsies in the fatal cases, the impression that it was a peculiar form of typhoid fever.

In the diagnosis of these fevers of continued type we have to take great care not only to distinguish them from other idiopathic fevers, but also from prolonged fever that may arise in connection with varied local conditions in which the febrile state, for the time, overshadows the local lesion. To pass the main of these in review: The most likely to be mistaken is the fever of miliary tuberculosis in instances in which the physical signs are not well pronounced. Indeed, the second case reported in this paper was regarded as acute tuberculosis by most of the many physicians that saw it. As a rule, the greater gravity of the constitutional symptoms, the emaciation, the sweats, the dyspnœa, the tendency to cyanosis, the cough, the signs of a diffuse bronchitis, the frequently present delirium, are conclusive. Still more so is the tubercle-bacillus in the sputum, though its absence in acute tuberculosis is, we well know, not positive proof of this malady not being before us; at times, tubercle-bacilli may be found in the blood when not detected in the expectoration.

Fecal accumulations may give rise to an irritative continued fever of weeks' duration. They are associated with heavily coated tongue and foul breath; often, too, there is some tenderness over the large intestine. The bowels are generally very constipated, but the reverse may happen, and then the resemblance, as in a case I saw with Dr. Arthur V. Meigs,[4] is really to typhoid fever rather than to prolonged cases of simple continued fever.

Anæmic fever, such as we sometimes meet with in chlorosis, much

[1] Southern Practitioner, December, 1891.
[2] Sajous's Annual, 1893, vol. i. H. 92.
[3] Transactions of the Association of American Physicians, 1893, vol. viii.
[4] Transactions of the College of Physicians, 1886, vol. viii.

oftener in pernicious anæmia, is another misleading form of fever. The look of the patient, the chemical and microscopical blood-tests, explain the irregular pyrexia, which I have seen, however, last several weeks at a time. Temperatures above 103° are extremely rare. The fever that may attend purpura, especially purpura hemorrhagica, is of the same kind; it may be continuous, but it is not high. By way of exception, hysteria is, at times, attended with continuous fever that is likely to show a distinct afternoon rise of temperature. Hysterical fever has been especially studied by French observers. It must be due to a disturbance of the functions of the heat-centres. Osler[1] reports a case that lasted over four years. We can only recognize hysterical fever by the neurotic history and the attending phenomena. There are nervous disorders in which prolonged fever also happens. It may be met with in chorea. In Goodhart's interesting article on "Innominate Fever,"[2] the case of a boy is mentioned who had protracted, irregular fever, and who had had chorea and possibly tetany, and left the hospital, after a six months' stay, with the fever uninfluenced. In all these fevers of nervous origin the temperature is apt to vary very much.

There are further groups of cases of organic change in which fever more or less continuous is observed; in persons, for instance, with rather rapidly advancing arterio-sclerosis, and in lithæmics. Then, too, we see cases in which there is organic disease, as of the endocardium, or of the lung or pleura, or duodenal catarrh, in which the lesion discernible is but slight, but in which, whether from slow absorption of morbid products, or idiosyncrasy of the patient, continuous fever is encountered. In cases of catarrhal pneumonia, or local plastic pleurisies, I have often known this happen. To this group, I think, belongs the case detailed by Chesman Barker,[3] in which fever lasting twenty-two days arose, without apparent cause, after an attack of pleurisy. In further instances, as in Hale White's[4] analysis of inexplicable pyrexia, albuminuria is found, and the question is raised whether the lesions are not due to the fever rather than the fever to the lesions. Connolly's[5] forty-four cases of continued fever consequent upon immersion in flood-waters, cannot, I believe, be regarded

[1] Practice of Medicine, second edition, p. 1029.
[2] Guy's Hospital Reports, 1888, vol. xxx.
[3] British Medical Journal, July, 29, 1893.
[4] Ibid., December 4, 1886.
[5] Australian Medical Journal, May, 1893.

as idiopathic continued fever, but seem rather to be catarrhal jaundice.

The protracted continued fevers do not happen in epidemics, nor are there relapses. Recurrences may, however, occur in the acute lithæmic fever, if such I may designate it. I have seen a case in the wife of a physician, with nine or ten attacks in six years, no one lasting over a week, but with very high temperatures, and very scanty urine. The point may well be made, as the attacks are short, not long, whether, strictly speaking, acute lithæmic fever ought to be here considered.

These continued fevers of long duration are, like the ordinary short simple continued fevers, almost never fatal; the form observed in the tropics has a less favorable prognosis than the other kinds, though there, too, the proportion of deaths is small. No lesions are found except congestion of internal organs. The spleen is not markedly enlarged. Slight meningeal exudation has been occasionally noted. I know of no accurate blood-examinations. It is a mere matter of surmise, in any of the varieties of the prolonged simple continued fever, what causes the fever. That it is due to a disturbance of the heat-centres seems certain. But what gives rise to this disturbance? Is it one cause, or are there several? Leaving out the hysterical cases and those of nervous origin, it appears to me likely that the fever originates from causes within the body; that either as the result of fatigue or overwork, or from impure water, or some preceding digestive disturbance, as happened early in both the very prolonged instances recorded at the beginning of this paper, leucomaïnes form from vitiated secretion, of a character to disturb the heat-centres. Whether in the continued fever of the tropics heat acts also in this way, or more directly, or through blood-changes produced, is a matter on which we can, with our present knowledge, only speculate. Both here and in all these prolonged continued fevers there is a great field for chemical research, especially in the leucomaïnes of the uric-acid group.

The treatment of the prolonged simple continued fevers is purely symptomatic. Quinine has no effect on them; nor have the ordinary antipyretics more than a temporary influence. Phenacetin and salol do the most good, particularly in cases with headache. They are best given in small doses, a grain or two, frequently repeated, until

their effect is manifest. Better still, where it can be efficiently employed, is the cold-bath treatment, not only to lower temperature, but for its revulsive and alternate influence. I regret that in the extremely long cases first mentioned circumstances prevented it from being thoroughly carried out. Purgatives, unless contraindicated by weakness, always form part of judicious treatment.

A CASE OF INTESTINAL AND HEPATIC ACTINOMYCOSIS IN MAN, ASSOCIATED WITH LEUKÆMIA.

By THOMAS S. LATIMER, M.D.,
OF BALTIMORE.

With Pathological Report.

By WILLIAM H. WELCH, M.D.,
OF BALTIMORE.

Wm. H. Thomas, colored, male, was admitted to the City Hospital on November 17, 1895. He was twenty-one years old, single, and did day labor. His family history was good so far as could be learned, except that one brother was said to have died of pulmonary tuberculosis. He had been in excellent health, except for the usual ailments of childhood, up to April of 1894, when he is said to have had appendicitis, which recurred in July and again in October of the same year. Why he was not operated on for the relief of the appendicitis I do not know, nor have I any knowledge of the particulars of these attacks.

The patient first came under my observation about November 18 or 19, 1895. He was at that time slightly anæmic, complained of headache, loss of appetite, and obstinate constipation, but was not so ailing as to care to keep his bed. On November 17th, the day he entered the hospital, the evening temperature was 101°, on the following morning 100°, while on the evening of the latter day it rose to 104°, falling next morning to 98°, and again in the evening rising to 104°, with another morning fall to 98° on the 20th, but rose the same evening to 100.2°, remained at that within a fraction of a degree throughout the 21st, and on the 22d went as low as 97.6°, rising only to 98° in the evening without further decline next morning. It continued variable throughout the rest of his life, but never again rose above 103.2° or fell below 98°. Slight chills and sweats were associated with these variations in temperature. His blood was several times examined for the malarial organism, with negative results. An examination of his chest discovered nothing wrong except a feeble heart-beat. His liver, however, was found greatly enlarged, extending well below the margin of the ribs, smooth, firm, and somewhat tender. No fluctuation could be found, but a tentative diagnosis of deep-seated hepatic abscess was made. Nothing further was discovered on extending the examination to the other abdominal organs.

On November 22d he was referred to the attending surgeon, who on the 23d aspirated the liver in several places without result; whereupon I resumed charge of the case. As I still entertained the opinion that an abscess was forming, yet not sufficiently advanced to yield pus on aspiration, he was put to bed, and saline cathartics were administered to relieve constipation. No particular suffering was for some time experienced except on lying on the right side or on manipulation of the liver. This organ continued steadily to increase in size, without presenting any circumscribed area of enlargement, tenderness, or fluctuation. The diagnosis of hepatic abscess was therefore soon abandoned.

The hospital case-book records on December 14th that "the patient is unable to lie on the right side without suffering, his mucous membranes are pale, appetite poor, he is uncomfortable after eating, and bowels continue costive. Slight general anasarca present. Heart-sounds feeble, pulse weak, soft and compressible, 120 per minute." The anasarca rapidly increased, together with fluid accumulation in the peritoneal cavity. Respiration now became considerably embarrassed, without indications of direct pulmonary involvement. This dyspnœa was of greater degree than was fairly to be accounted for by interference with the movements of the diaphragm or any recognized pulmonary lesion. The respiratory difficulty, feeble heart and pulse and pale mucous membranes, with frequent nose-bleeding, suggested an examination of the blood, which was accordingly made with the following result:

Red corpuscles	3,200,000
White corpuscles	246,000
Small mononuclear leucocytes	3 per cent.
Large mononuclear and transitional leucocytes	4 " "
Polynuclear-neutrophiles	58 " "
Eosinophiles	5 " "
Myelocytes	30 " "

Proportion of white to red corpuscles 1 to 13. Hæmoglobin 25 per cent. Slight enlargement of the axillary and post-cervical lymphatic glands was now observed, but beyond this no lymphatic involvement was detected throughout the disease. Repeated examinations of the region of the spleen were made without the discovery of appreciable enlargement. The ascites was several times relieved by tapping, which added much to the comfort of the patient. Advantage was taken of the relaxed condition of the abdomen after tapping to search for the spleen, but at no time could I palpate it.

The blood examination, especially the large number of myelocytes, together with the very slight lymphatic and splenic involvement, led me to the conclusion that it was a case of almost pure myelogenous leukæmia, and that the enlarged liver was due to diffused leukæmic infiltration, as in the case described by Welch, in which the liver

attained a weight of over thirteen pounds. The patient was accordingly presented to the class, and his symptoms were considered from this point of view.

Nothing was observed in the mouth except a furred tongue at times, and extreme pallor of the mucous membrane. The teeth were white and sound, the tonsils normal, and the maxillary bones presented no surface change to attract attention, nor did the patient at any time make complaint of his mouth. No suspicion of actinomycosis was entertained, nor can I now see in reviewing the clinical history anything that could have suggested such a condition. It is possible that had an examination been made of whatever small particles were found clinging to the aspirator needle, the microscope might have cleared up the diagnosis. No such examination, however, was made.

It will be observed that at no time, while the patient was under my observation, was there anything to indicate a present appendicitis. No marked tenderness except over the liver; no lump; no intestinal disturbance except a tendency to constipation, easily relieved by cathartics without increase of pain on defecation. If any symptoms to indicate involvement of the appendix were present, they were completely masked by the condition of the liver, the ascites, and the œdema of the abdominal walls. Varying degrees and sites of pulmonary œdema were repeatedly observed during the progress of the case in the last six weeks of life, which added greatly to the respiratory labor, but which measurably diminished at times, notably after the tappings.

When the diagnosis of leuksæmia was made the muriated tincture of iron, with Fowler's solution of arsenic, in twenty and five minim doses respectively, were directed. Milk punches were given three times daily, and he drank freely of milk, of which he was fond. He was not restricted to fluids, however, and at times ate the ordinary hospital fare with apparent relish, although in general his appetite was not good. As his heart was conspicuously feeble, digitalis was several times prescribed, but as this did not agree with him, strychnia sulphate, $\frac{1}{30}$ gr. three times a day, was substituted with better effect. Occasional purges were given to relieve constipation and with the hope of reducing the dropsical effusion, but with little or no effect so far as the latter was concerned, and owing to the feeble condition of the patient it was not thought expedient to persist in their use. Except the occasional administration of hypnotics and anodynes to procure sleep and relieve pain and dyspnœa, nothing further was done.

On January 15th he was tapped for the last time, with considerable relief to the dyspnœa, but for a few days only. His strength diminished steadily until February 10th, when he died, apparently from asthenia.

Autopsy about five hours after death by Prof. N. G. Keirle and Dr. John Rurah. Body of medium-sized man, development slight. General anasarca. Œdema is greater on left side of the body, face and arms especially. Skin pits on pressure everywhere. Over arms and legs fingers can be pressed in

2 cm. without difficulty. Abdomen very much distended with fluid. Thin, watery fluid running from mouth and nose. Adipose tissue scanty, and almost white in color. Blood running from veins on incision is thin and watery, and lighter in color than normal. Muscles pale and bloodless. Abdomen contains a large quantity of pale, straw-colored fluid; cavity divided into numerous spaces by adhesions, all filled with fluid. Pericardium contains about 75 c.m. of straw-colored fluid, visceral layer pale, almost white, glistening throughout. There is considerable serous effusion beneath it, giving a marked œdematous appearance. This is principally around the junction of the auricles with the ventricles. Over the left ventricle chiefly, but also over other parts of the heart surface, there are small ecchymoses about 1 mm. in diameter. Parietal layer of pericardium is white, bloodless, and glistening throughout. Heart and lungs together weigh 2190 grms. Heart weighs 340 grms. White "milk patches" on the surface of right pericardium. All cavities of heart are empty. Tricuspid orifice 33 mm. in diameter. Valve transparent, no thickening. Pulmonary artery 25 mm. in diameter. Valve transparent and perfect. Mitral orifice 31 mm. in diameter. Valve transparent throughout, with slight tendency to ground-glass appearance. Aortic orifice 23 mm. in diameter. Valve shows slight, opaque, thickened patches. Heart muscle pale and of a peculiar, translucent appearance, but no degeneration apparent to the naked eye. Coronary arteries, walls pale, otherwise normal. Thoracic aorta shows changes of slight endarteritis.

Left pleural cavity contains 500 c.c. of pale, yellowish fluid; no adhesions. On right side a few adhesions, that break up easily, between visceral and parietal layer of lower lobe. There are a few firm adhesions between lower lobe and diaphragm. Right lung pushed up to fourth rib in front, but extends in back to tenth rib. No effusions on right side. Left lung slightly pigmented, upper lobe crepitates, oozes white frothy fluid on section. Lower lobe does not crepitate in lower half, oozes a thin sanious fluid on section. Pieces sink in water. Upper lobe slightly emphysematous. Right lung also crepitates, oozes pale serum on section, upper lobe somewhat emphysematous. Middle and lower lobe solid, ooze a bloody, but pale, serum on section, not at all frothy. Pieces sink in water.

Peritoneum generally thickened, both parietal and visceral layers. Intestines bound together by peritoneal adhesions. These adhesions are divided off by numerous small spaces, all filled with fluid. Omentum very adherent and without fat; extending from right iliac fossa along right margin of the abdominal cavity to the liver, which extends some 10 c.m. below the margin of the ribs. Along the costal margin to 7 c.m. of the median line is a dense, firm mass of organized inflammatory tissue 3 c.m. in thickness. At the lower part of the same, pus escapes, on cutting out the mass, from a cavity that could not be well determined, as it was all closed in by thick walls of inflammatory tissue. Just below the liver about 25 c.c. of greenish-yellow pus escapes from an abscess at that point.

The spleen is slightly enlarged, weight 350 grms., surface bluish-gray.

Post-mortem discoloration on lower aspect; capsule slightly thickened. Spleen substance firm and the color of healthy muscle. Malpighian bodies distinct. Trabeculæ not very well marked.

Left adrenal is slightly enlarged, firm, color of healthy muscle, pigment not very dark. Right adrenal is found flattened against the liver, of brownish color, otherwise normal. Left kidney weighs 270 grms. Capsule distended with fluid, almost fell from the kidney when opened. The surface of the kidney is moderately red. Stars of Verheyen show distinctly. The cortex on section is 1 c.m. thick and irregular. Oozes a pale bloody serum. Cortical vessels indistinct. Glomeruli distinct, but pale and colorless. Irregularity in thickness of cortex apparently due to malformation. The kidney is triangular in shape, base of triangle in the pelvis. It has a swollen look, apparently cloudy swelling. Right kidney corresponds to the left, but is more regular in shape and more œdematous.

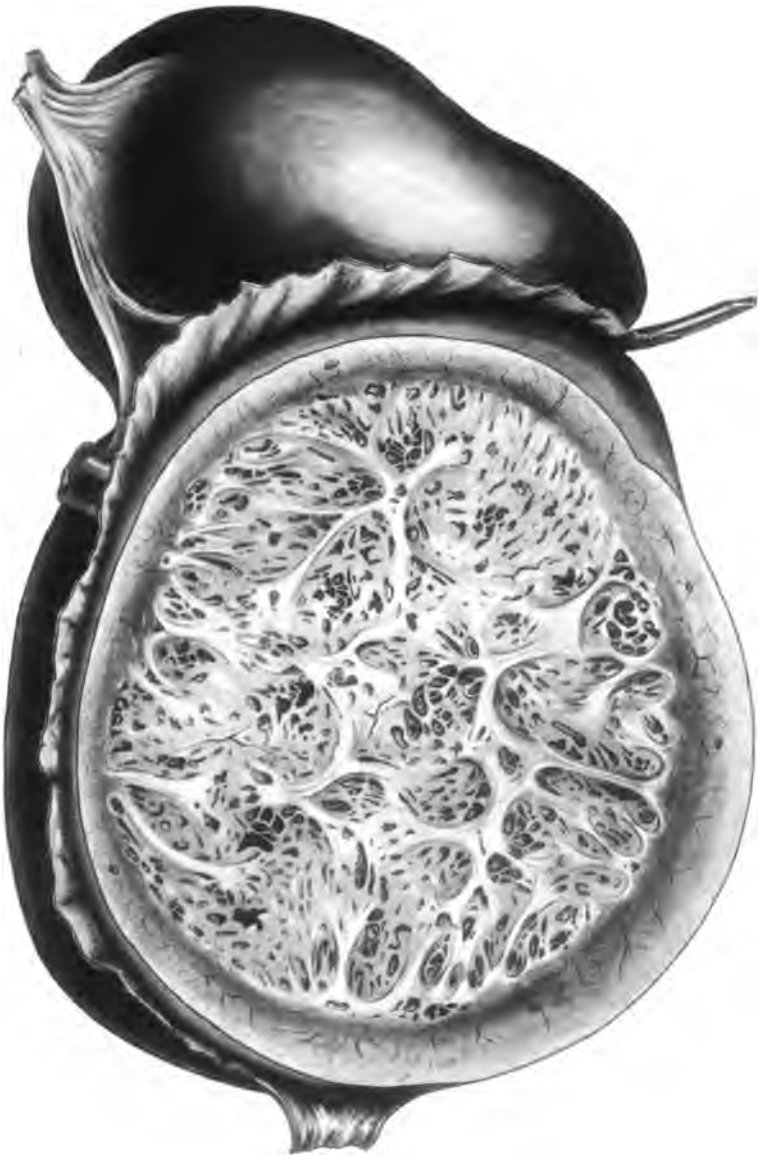
Bladder moderately distended with about 200 c.c. of urine. Its mucous membrane is very pale. Both testicles extremely pale and œdematous, with small surface cysts. Tunica albuginea remarkably white. Mesentery markedly œdematous. Sigmoid flexure and the remainder of colon to middle of transverse portion apparently normal. The entire ascending colon and the hepatic half of the transverse colon are massed in inflammatory tissue. The ascending colon, for 6 c.m. in its middle could not be removed, is black from post-mortem discoloration. The appendix is involved in a mass of inflammatory tissue just above the brim of the pelvis. Peyer's glands are distinct and present a shaven-beard appearance. Bile duct patent. Liver weighs 3260 grms. An examination of the marrow taken from the long bone of the leg shows both macroscopical and microscopical changes characteristic of leukæmia, but nothing to suggest actinomycosis.

Examination of the Liver, by Dr. W. H. Welch.

The liver was the only part submitted to me for examination. It had been incised, but was complete. It was preserved in alcohol.

Macroscopic examination. The liver presents an irregularly globular shape, measuring 22 x 18 x 12 ctm. The right lobe, which is much enlarged, is occupied throughout nearly its whole extent by a mass measuring 12 x 16 ctm. This mass extends for a short distance also into the left lobe. It extends throughout the whole thickness of the liver, from the lower to the upper surface, but it occupies a larger transverse area in the lower two-thirds than in the upper third of the organ.

The inferior surface of the right lobe, with the exception of a narrow margin of liver-substance on the right side, is entirely occupied by the new growth, which here was apparently continuous with an abscess formation extending downward along the ascending colon. This inferior surface and the posterior margin of the right lobe are connected with a dense mass of fibrous adhesions, in which are included the hepatic vessels, the right adrenal gland, and the hepatic flexure of the colon.



Transverse section of the liver, showing the honeycombed appearance of the actinomycotic tumor of the right lobe and the fibrous capsule enveloping it.

The diaphragm is firmly adherent to the superior surface of the right lobe of the liver, and has been removed with the liver. The mass of new growth in the liver has penetrated through the liver-substance on the upper surface, but has not penetrated through the adherent and thickened diaphragm.

Upon section it is seen that a definite fibrous capsule of dense consistence and grayish color surrounds the mass in the liver, separating it from the surrounding brownish-red parenchyma of the liver. This fibrous capsule is complete except in certain areas on the inferior surface of the liver or of the new growth, where the opaque, yellowish characteristic foci of the mass come to the surface, and were evidently in connection with the subhepatic abscess. This relation and the general topography afford presumptive evidence that the morbid process invaded the liver from below by continuity.

Upon section the mass presents in exquisite manner the characteristic honey-combed appearance of a chronic actinomycotic tumor, as is well shown in the accompanying plate. There are spaces and interlacing trabeculæ. The spaces often anastomose. They vary in shape and size on section, some being round, others oval, others more or less cylindrical. They contain a soft yellowish-white purulent material, which can be squeezed out readily, and in which can be detected abundantly the small yellowish granules of the colonies of actinomyces. The immediate margins of the spaces are of an opaque, yellowish-white, necrotic appearance. The spaces vary from 1 to 6 or 8 mm. in diameter.

The trabeculæ are in general broad and interlacing and of firm consistence and translucent gray color, like fibrous or granulation tissue.

Microscopic examination. For the study of the histological structure, staining with hæmatoxylin and eosin was used; for the details of the structure of the parasite, Gram's, Weigert's, and Mallory's stains were found most serviceable.

The microscopical sections show interlacing bands of fibrillated connective tissue, rich in long fusiform cells. Between these fibrous bands there are dense accumulations of cells. In the immediate neighborhood of the actinomyces the cells are closely packed together and there is little or no basement substance. These cells are predominantly polynuclear leucocytes; in other words, the parasitic colonies lie for the most part in purulent foci. Outside of the areas of actual pus there is granulation tissue in varying stages of formation, from a tissue composed almost exclusively of granulation cells and leucocytes to a tissue rich in basement-substance and with elongated cells. In the fibrous trabeculæ are bloodvessels with thick muscular walls, and containing an excess of leucocytes, among which are many mononuclear forms. Adjacent to the liver parenchyma the fibrous tissue is dense and contains numerous rows of compressed liver-cells, presenting the appearance of the so-called newly formed bile-ducts. Here and there are mucous glands derived from those in the walls of the bile-ducts, but now without evident connection with bile-ducts, and apparently hypertrophied

and proliferating so as to simulate adenomata. The capillaries of the liver contain an excess of leucocytes, mononuclear cells predominating.

The colonies of actinomyces are rarely single, more frequently they are conglomerated into irregular masses, which may be 1 to 2 mm. in diameter. These colonies in general present a central, looser part of tangled fine filaments and slender rods, with, at times, deeply staining coccus-like bodies, and a more densely woven ring of fine filaments nearer the periphery, from which the filamentous branching threads radiate outward. These radiating threads often extend out among the surrounding pus-cells and are often devoid of any bulbous swellings or club-like extremities.

It was not found easy to demonstrate satisfactorily the clubs which are frequently found at the extremities of the threads in cases of actinomycosis. The stain recommended by Mallory is most suitable for this demonstration. By this stain there could be demonstrated around some, although not around most, colonies a deeply stained red, almost homogeneous, peripheral zone, into which the blue threads could be traced. This red margin clearly belonged to the parasite and not to the surrounding cells, from which it was often separated by a narrow space. The outer surface of this red border was often somewhat irregular and indented, and in general the impression was gained that this outer zone, which stained by Mallory's method deeply red, consisted of the coalesced material which composes the club-like swellings at the extremities of the threads in most cases of actinomycosis. I am inclined to interpret the failure to demonstrate sharply defined clubs in this case, and the appearance of a diffuse, homogeneous, peripheral substance, with the staining reactions of the clubs, to post-mortem changes. That the clubs may become indistinct or even disappear in consequence of post-mortem changes has been demonstrated by Weigert.

But only some of the colonies showed this homogeneous marginal zone. Many were entirely devoid of such a zone or of any suggestion of clubs. It is now well known that actinomyces colonies are often devoid of the characteristic club-like swellings. In this case, as in that reported by Mallory, there were numerous bacilli belonging to the actinomyces, scattered among the cells independently of the colonies. Clumps of streptococci were also observed in small number, so that there was mixed infection with actinomyces and streptococcus.

The mass in the liver, therefore, presents macroscopically and microscopically the typical structure of an actinomycotic tumor. As has already been stated, the evidence is that the parasite gained access to the liver and generated the new growth at the inferior surface of the organ. The process gradually extended so as to invade most of the right lobe and a part of the left lobe of the liver.

Although I have not had the opportunity to examine other parts from this case, there can be little or no doubt, in the light of the clin-

ical history and the observations made at the autopsy, and in similar cases, that the portal of entry of the parasite was the intestine, and in all probability the starting point was actinomycotic appendicitis (possibly colitis), whence the morbid process extended upward in the tissues along the ascending colon to the right hypochondrium, and invaded the liver at its lower surface. (End of Dr. Welch's report.)

The coexistence of leukæmia with actinomycosis has not, I believe, been noted, and it would be of interest to determine if they may sustain any etiological relation to each other. I cannot find in any of the reports that have come to my notice any reference to examinations of the blood in actinomycosis, except for the specific organism, which has not, I believe, been found in it. Nor do I find any reference to general conditions analogous to those occurring in leukæmia that might not be accounted for as the result of the local development. It seems rational, therefore, to conclude that this complication was purely accidental. It must, however, have told very much on the progress of the case, no doubt hastening the end and adding materially to the suffering of the patient. The labored breathing, although in part accounted for by the condition of the left lung, the small pleuritic effusion, the recurring pulmonary œdema, the pressure of the liver and of the ascitic fluid, was doubtless largely due to the defective oxygen-carrying capacity of the blood. So no doubt the unusual extent of the dropsy, affecting nearly every organ and tissue of the body as it did, was rather of leukæmic than actinomycotic origin. No board-like œdematous infiltration such as has been noted with pulmonary actinomycosis was observed, but everywhere a diffuse serous infiltration of ordinary character.

To the leukæmia must also be referred in great part the marked feebleness of the patient beyond what is usually observed in actinomycosis, although this was also to some extent due to the septic condition, of which the alternating irregular fevers, chills, and sweats were indications.

The mode of entrance of the infecting organism in this case seems clearly to have been by the alimentary canal. The parasite effected a lodgement in the vicinity of the appendix, where its primary development occurred. This conclusion is warranted by the post-mortem observations as well as by the clinical history and by

previous reports of cases of actimycotic appendicitis. The patient, living alternately in the country and in the city, was no doubt while in the former in position to acquire the habit of carelessly chewing grains and other vegetable matter, and may have been in close association with infected cattle; but as no suspicion of the real nature of the trouble was entertained during his life, nothing was learned tending to show clearly the source of infection. There is strong reason for doubting whether the disease may be directly communicated from cattle to man by simple contact; indeed, inoculations of lower animals have been attended with such imperfect success as to make this source of infection unworthy of belief. No case of direct transmission, even from cow to cow, has been shown. Nor is there any evidence that the disease may be acquired by eating the flesh of infected animals, and the fact that its existence has been reported in but one of the carnivora—a dog—goes far to show that this is a most unlikely mode of propagation. The same may be said of milk as a source of infection. Bollinger had one case, primary in the brain, attributed by him to milk infection.

The disease has rarely been observed on the udder or teats of cows. Leith[1] refers to an interesting case of infection of the milk glands of the cow, which he was enabled to examine through the kindness of Prof. Mettam, in which the characteristic elements of actinomycosis were found lying among the galactophorous ducts, which, however, they did not invade. The tubes, notwithstanding, showed marked signs of disease, "their living epithelial cells being greatly swollen, staining badly, and being without nuclei. There is also in places a considerable amount of interstitial round-celled infiltration. It is thus seen that the actinomyces does not itself apparently directly invade the gland tubes in this case. It produces a considerable change in them of a hurtful character, and further, that it is difficult to believe that the parasite does not in some form or other directly invade the tubes, as the two lie so close together and are so intermingled."

Against its transmission to human beings by milk—the possibility of which must be admitted—is its extreme rarity in early childhood. Only four cases in Leith's series of 378 cases occurred prior to the fifth year, and only seven up to the tenth year.

[1] Edinburgh Hospital Reports, vol. ii. p. 179.

The great majority of the cases in which source of infection has been definitely established have been of vegetable origin, as in eleven cases of Boström—referred to in the *Edinburgh Hospital Reports*—in which he found in the primary local lesion grains of barley or corn or other cereals, with the actinomyces growing abundantly in and from them. Johne, in 1881, demonstrated actinomyces in vegetable substance found in the tonsils of pigs; four years later Boström and Pianá separately made the same demonstration in the tongues of oxen, and in 1888 Brazzola, and in 1889 Hofmann, "made similar observations, the latter in a case of the disease in the pharynx of a man."[1]

Even in the lower animals actinomycosis is practically confined to ungulates—oxen, horses, pigs—with the single case among carnivora, reported by Vachetta, in a dog, to which reference has already been made.

Mossbrugger's statistics show that of seventy-five cases only ten were peasants, and of these but two had care of cattle.[2] In thirty-eight cases reported by Israel not one was engaged in the management or care of cattle. The far greater frequency with which the mouth and adjacent regions are the seat of the primary affection shows pretty conclusively that the infecting organism is received with the food or drink. Rütimeyer records 50 per cent. in head and neck, 25 per cent. in lungs, 15 per cent. in intestines, 15 per cent. indeterminate.[3]

The intestinal cases were in all probability derived from food, and even those of primary pulmonary origin may have had a similar mode of entrance, although of these the possibility must be admitted that the organisms were air-borne on bits of chaff or beards of cereals.

The facts that the actinomyces has not been found in milk nor in water, that the cooking of meat would destroy it, that the disease is more common in Germany, where the meats are well cooked, than in France and in England, where they are more frequently eaten rare; that it occurs in herbivorous and not in carnivorous animals; that although the parasite has not been positively identified in connection with vegetable matter outside the animal body, it has frequently been so found in the site of disease in the human and in lower animals, all go to make up a strong body of evidence in favor of its purely vegetable origin.

[1] Leith, loc. cit. [2] Cherétin, Medical Week, February 1, 1895. [3] Leith, loc. cit.

Leith's list of 100 cases, showing the relative frequency in different occupations, lends strong support to the view that it is likely to be introduced with food into the human body. "Of these 10 were coachmen or grooms, 32 peasants or workers in the field (only 5 of whom were employed about cattle), 25 were farmers, grieves or land-owners, 8 bakers or millers." Thus 75, or three-fourths of the whole number, were engaged in pursuits in which they would be likely to acquire the habit of carelessly chewing those grains with which the parasite has alone been found associated in the human body.

By far the largest proportion of cases has been found in men and in the third decade. Nearly three men to one woman have been affected with the disease, the sex most given to field-work and at the age when men are most actively afield.

There is every reason to believe that this case was of primary intestinal infection, of which class a considerable number has now been reported. Rütimeyer gives 15 per cent. of intestinal cases, but Leith, from the records of 430 cases, found 21⅜ per cent. of abdominal cases, with 55¼ per cent. in the head and neck. Any part of the alimentary canal may be affected, but the stomach with comparative infrequency; from which it may be inferred that the acid gastric juice affects the parasite unfavorably, and that intestinal infection is due, as suggested by Leith, to the protection afforded the parasite by the "grain coats" while in the stomach.

It is not surprising that intestinal cases should be attended with so great a mortality, owing especially to the difficulty in diagnosis, for since the use of potassium iodide in this affection has become more common a sufficient number of cases successfully treated has been reported to strongly support its claim to curative properties in actinomycosis. But it is only where there are primary surface lesions or when deep-seated lesions have made their way to the surface by ulcerations, or by discharge into the lumen of some natural outlet, as of the bronchial tubes or intestinal canal, so as to make the infectious agents of the disease available for inspection, that the diagnosis can be made, or, indeed, be reasonably suspected. There are absolutely no symptoms distinctive of the disease or very strongly suggestive of it. Accident may reveal it, as perhaps in this case it might, had the aspirator tube, when puncturing for supposed abscess, been examined; or had an operation been done for the appendicitis and a microscopic

examination been made. Possibly repeated examinations of the stools, as in the case of Ransom, where detection of actinomyces in the dejecta revealed the nature of the case, would have revealed its true nature. But in the absence of suspicion of the nature of the trouble such examinations are not likely to be made, and where made by one without previous familiarity with the microscopic characters of the parasite they are likely to be without result.

Perhaps nothing is more strongly distinctive of actinomycosis than its chronicity and the absence of constitutional symptoms except such as are incident to pus formation (believed by many to be accidental from associated pyogenic organisms), or the result of distinctive changes in important organs by the local development—symptoms however which do not differ in any way from those in similar conditions, however produced, and are therefore nowise distinctive of actinomycosis.

In the case under consideration I am unable to point to one single feature that was of diagnostic or even of suggestive value as regards actinomycosis. There is, in short, in the present state of our knowledge, absolutely no way of diagnosing this affection when in abdominal, thoracic, or pelvic organs, until some portion of the product of the activity of the actinomyces or the parasite itself is before us for inspection. Grave doubts may be entertained as to the pathognomonic significance of the wooden œdema of the thorax, upon which emphasis is laid by Netter in the diagnosis of pulmonary actinomycosis.

DIAGNOSIS OF DILATATION OF THE STOMACH.

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THE diagnosis of dilatation of the stomach meets with two difficulties at the very outset: first, the class of cases to which the term is applicable, and, second, the difficulty of determining the lesser grades on account of the variability in the size of the normal organ. It would seem simple enough to decide what class of cases belong properly to this group of diseases; but practical experience leads us to believe that, though the diagnosis is made with unwarrantable frequency by those who are guided by superficial examination and by clinical symptoms, often not at all distinctive; those who have pursued their studies from the modern scientific standpoint, on the other hand, withhold the diagnosis in certain instances in which a careful consideration of the whole subject would warrant the application of the term under discussion. The group of cases to which the latter observation has special reference is that designated atony of the stomach or motor insufficiency.

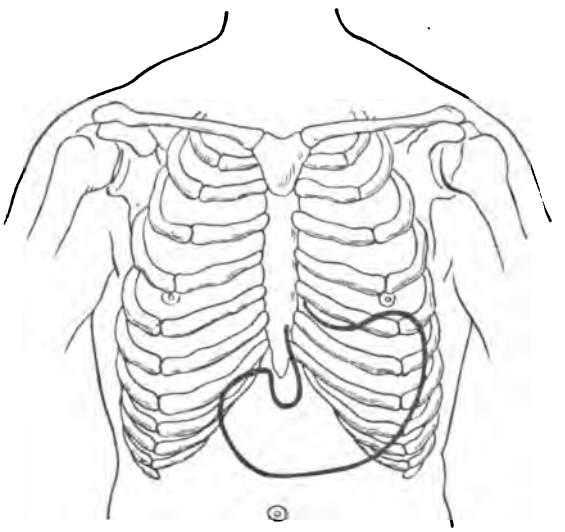
All writers, it is true, have recognized forms of dilatation dependent upon atony of the muscular walls of the stomach, but it has been customary to apply the term atonic dilatation to cases in which the process is well advanced, reserving the names motor insufficiency and simple atony to cases supposed to represent loss of motor function without change of size of the organ. This view, we believe, is incorrect and founded on too narrow a consideration of the conditions present in the stomach. There are doubtless cases of chronic interstitial in-

flammation of the stomach, or perhaps even of ordinary chronic gastritis, in which the organ is not enlarged and yet in which the motor function is diminished, just as there are cases of chronic interstitial myocarditis without cardiac dilatation and in which the heart power fails; but the term atony of the stomach is here considered rather as applying to cases of neurotic or degenerative weakness of the muscle itself, and in such cases we hold there is and must be from the first some, though possibly little, dilatation, just as in cardiac weakness due to obscure disturbances of innervation or to degeneration of the muscle-fibres a certain amount of dilatation must exist. Beginning with a primary disease or atony of the muscle of a hollow viscus there is, of course, a period when no enlargement has occurred, but this period is practically of no duration, for the very first evidence of the disease must, as a matter of course, be due to relaxation—that is, enlargement or dilatation. We hold, therefore, that what is termed atony of the stomach is merely a beginning stage of actual dilatation, which may or may not progress, and that it should be so classified.

When, however, we approach the second difficulty alluded to, viz., the determination of the existence of dilatation in the anatomical sense by actual demonstrative methods, we at once realize the comparative inutility of all the plans proposed. The matter would be simple enough if it were possible to assign any definite limits to the normal organ or to determine a normal capacity, but both of these are impossible tasks. As far as the normal outline and position of the stomach are concerned, we are quite firm in the belief that Luschka's original assertions represent the average conditions. Luschka's outlines will be sufficiently represented by the accompanying figure. It will be noted that the pylorus lies in the angle between the right border of the xiphoid cartilage and the right costal margin, that the lower border or greater curvature is well above the umbilicus, and that the fundus lies beneath the base of the left lung and almost completely covered by its projecting margins. There is doubtless considerable movability with the respirations and with increased or decreased amounts of food; but the general points agree very closely with our observations in post-mortem examinations; and the latter, we may assert from our own experience in cases studied during life and post-mortem and from the recent investigations of Meinert, furnish reliable indications of the position of the organ during life. We cannot, therefore, agree with

those (Martius, Meltzing, and others) who assert that the normal position of the inferior margin of the stomach is as low as the umbilicus or lower. Such views, we are convinced, are based upon either unreliable methods or upon the study of cases of downward dislocation of the pylorus or the abnormal vertical position of Kussmaul. In these latter cases the stomach is not of necessity enlarged, though this may frequently be the case; but in any event it is to be noted that when the lower margin of the organ lies near the umbilicus or below it, and is due, in the main, to dislocation, a corresponding dislocation of the

FIG. 1.



Normal position of the stomach. (After LUSCHKA.)

pylorus and of the lesser curvature may be expected. When, on the other hand, there is actual dilatation of the stomach the lower margin is similarly placed, but the lesser curvature and pylorus are then much less displaced. Some dislocation does occur in nearly all cases of dilatation excepting such as are complicated with adhesion to the liver and other structures; but the downward displacement of the lower curvature is far in excess of that of the lesser curvature and pylorus in cases in which the dilatation is the principal or primary condition and the dislocation merely subsidiary or secondary. To this extent the

study of the normal position of the stomach is, in our estimation, of value, and the recognition of the vertical position as an abnormal one of importance.

The second point concerning the anatomy of the organ to which we have alluded as offering difficulties in the recognition of dilatation is the size of the organ. That this varies greatly in different individuals would seem to require no special demonstration, but studies have been recorded which indicate how great a variability exists within the limits of what may be termed normal structure. In the casts made under the direction of v. Ziemssen it was found that the difference in shape, as well as size of the stomach, was very considerable in persons of about the same size; and Pacanowski found great variations in the area of gastric tympany in eighty-one cases. In Ziemssen's series the capacity of the organ was determined by filling specimens with water, and was found to fluctuate markedly, the greatest capacity, however, being 1680 c.c. We have ourselves made studies in the same direction, taking cases in which no suspicion existed of gastric disease. The stomach in each case was filled with water under a pressure of about 25 cm. (part of the œsophagus being left attached). The smallest organ was found in a boy of nineteen years, 1.73 m. in height, who had died of pulmonary phthisis. The stomach in this case held but 500 c.cm. of water. The largest stomach was found in a woman of twenty-nine years, of rather delicate construction, and 1.55 m. in height. In this case the stomach held 2600 c.cm. In the other cases the capacity varied greatly between these limits, that of a number being over 1680 c.cm.—Ziemssen's maximum. It may further be observed that Beneke's figures also indicate a far greater capacity than do those of Ziemssen; but, after all, it is evident that the variability in the size of the stomach is too great to permit of absolute limits even for the maximum size of what might be considered a healthy organ.

The mere question of size has therefore lost much of its old-time significance as an indication of dilatation, and Ewald, Riegel, and others very properly call attention to the fact that all of the physical signs of enlargement of the stomach may be present without any evidence that there is functional insufficiency. To this condition Ewald has given the name megastria or megalogastria. Enlargement of the organ of such degree that it may clearly be spoken of as in excess of

the maximum size found in ordinary healthy individuals cannot at once be termed dilatation. There must always be evidences that the motor power is deficient and that stagnation of food is taking place. It is going a step too far, however, to dispose entirely, as Boas does, of the term dilatation and to classify all cases under the heading: Gastric Insufficiency, of the first or the second degree. Dilatation is a pathological entity not to be set aside in this manner, and though we agree with Boas in the important part he assigns to the want of motor power, we cannot agree that the latter should be made the basis of classification. There are undoubtedly cases of actual and sometimes considerable dilatation of the stomach in which the motor power has been augmented almost or quite to the point of restoration of sufficiency at first impaired by pyloric obstruction. A classification based entirely upon the study of the motor function would fail to include such cases among the pathological conditions of the organ, though in but a short time rupture of the compensation might occur and the cases might at once fall into the category of insufficiency of the second degree or of great gastric dilatation. Boas's classification owes its origin, we believe, to a recognition of the difficulty of determining whether the size of the organ has become augmented or not, but this is a difficulty that must be overcome and not evaded.

From these preliminary remarks we may conclude that the term dilatation of the stomach is to be applied to a greater number of cases than has usually been admitted, and that in particular the condition known as simple atony or motor insufficiency is really an early stage of dilatation; that the mere determination of the size of the organ is not to be considered a reliable indication of dilatation, though, on the other hand, the importance of enlargement must not be overlooked.

We would classify all cases in two groups, designating these as *atonic dilatation* and *obstructive dilatation*, respectively. We would reject the term mechanical dilatation, since certain cases of dilatation are essentially mechanical, in that they result from traction upon the walls of the organ, and yet are not mechanical in the sense in which this term is ordinarily applied, viz., as indicating pyloric obstruction. It is not our purpose to speak exhaustively of the causes of dilatation of the stomach, but we wish rather to review briefly the principal conditions giving rise to this disease.

Atonic dilatation may occur in two ways: first, by primary or ab-

solute atony of the walls, and, second, by secondary or relative weakness. Primary atony of the walls with atonic dilatation of slight degree is a much more frequent condition than has been generally believed. It may occur in persons of relaxed fibre, in nervous, anæmic, or debilitated conditions, resulting from a variety of causes; or, on the other hand, it may be a complication of chronic or even of acute gastritis. In rare cases, as in those of Fagge, Endmann, Oser, Kundrat, and Boas, atonic dilatation may be acute, and in such instances it is prone to be serious. Some of these cases, however, are doubtless obstructive, the pyloric stenosis being due to spasm, the result of acute indigestion or hyperacid secretion. Usually it is a slowly progressive or a stationary process, largely influenced by the general conditions of the patient's system.

In the group of atonic dilatation due to relative atony of the walls may be included the cases in which overeating and drinking are responsible for the disease. In such cases the constant strain of large amounts of food gradually induces relaxation and enlargement; and it is likely, also, that hypersecretion and hyperacidity are first set up, and that these are largely the cause of the subsequent dilatation, being active in the way of causing pyloric spasm, or even hypertrophic thickening of the pyloric ring. Another form of relative atony of the walls of the stomach is that produced by adhesions or by the dragging of the omentum in corpulent persons. In such cases the natural tone of the stomach walls is overcome and more or less relaxation ensues. Somewhat similar conditions are present in cases in which cicatrices of gastric ulcers occupy parts of the stomach removed from the pylorus. There results a weakening of the walls of the organ, which terminates in dilatation.

The group of obstructive dilatation of the stomach comprises the cases dependent upon pyloric stenosis, whether this be organic or functional, and due to disease of the pylorus itself or to outside causes. It is scarcely necessary to make more than passing mention of the causes of organic pyloric obstruction. Carcinoma and cicatrices of pyloric ulcers are the important forms of stenosis; but occasionally other neoplasms or hypertrophy of the pyloric fibrous or muscular tissues may be active. Among the rarer neoplasms causing obstruction, we have seen a myoma of the muscularis which projected into the stomach and acted like a ball-valve, very much as, in certain rare

cases reported in the literature, peach-stones or other foreign bodies have acted. In another case under our observation, the stenosis was caused by an infiltrating sarcoma. A number of times we have seen the pylorus occupied by a ring of fibro-muscular tissue somewhat resembling, in its macroscopic appearances, a scirrhous cancer. In such cases there has generally been a history of painful disorder of digestion and of constant hyperacidity, and we have no doubt that frequently repeated spasms, probably combined with inflammatory attacks, account for the formation of such hypertrophic conditions. Among the cases of so-called annular myoma of the pylorus, many no doubt belong to the cases here referred to. Repeated spasm may, however, result in dilatation without notable organic change at the pylorus. The antecedent causes which occasion spasm may be various. Hyperacidity and hypersecretion, and these in turn often dependent upon overeating and alcoholic excesses, have been referred to. Acute and painful ulcers near the pylorus may act in a similar manner, and possibly displacement of the kidney or other abdominal diseases may give rise to reflex pyloric contraction.

Dislocation of the stomach, and especially the extreme vertical position, may cause a mechanical obstacle to the discharge of the gastric contents from the position alone, and a more serious obstruction in the form of a sharp angulation of the horizontal portion of the duodenum, or of the junction between the stomach and duodenum.

The causes of pyloric obstruction outside the stomach itself are very numerous. Tumors may compress the pylorus, or, as in one of our cases, inflammatory adhesions may bind it firmly to the head of the pancreas and the posterior abdominal wall. Some attention has been called to displacement of the right kidney as a cause of dilatation by Bartels, Malbranc, Schütz, Litten, and others, and one of the cases here reported by us, belongs in the same class. We do not feel warranted in asserting that the gastrectasis in such cases results entirely from pressure upon the duodenum, nor, on the other hand, does it seem likely that the conditions are wholly coincidental. A consideration of the anatomical relations permits the suspicion that injurious pressure upon the duodenum might result from moderate displacement of the right kidney, especially if such displacement were due to downward and inward pressure of the liver, resulting from tight lacing. Some authors have urged that the very movability

argues the unlikelihood of serious pressure occurring in this way; but with a moderately movable kidney the conditions are just such, we would urge, that so long as the thoracic compression is continued the kidney is forced against the vertical portion of the duodenum. It has further been claimed that the peristaltic movements of the intestines are so active that the pressure of the kidney could scarcely cause obstruction. To this we would reply that the portion of the duodenum pressed upon by a displaced kidney is one of the least movable parts of the entire tract, being quite firmly attached by the reflection of the peritoneum lying in front of it. While for these reasons we are still disposed to believe that displacement of the kidney may occasion gastrectasis by direct pressure upon the duodenum, we are also inclined to believe that other causes act at the same time. Thus simultaneous gastric and visceral descent may cause angulation and compression of the duodenum, while reflex nervous spasm of the pylorus or neurotic relaxation of the entire organ may be the principal or the contributing causes in some cases.

DIAGNOSIS. The ultimate diagnosis of dilatation of the stomach must rest upon the recognition of deficiency in the power of the stomach to propel its contents into the intestine and upon the discovery of enlargement of the organ; but there are numerous features presented in the disease of a more or less significant character, which are discovered in a systematic examination by the methods of physical investigation. In very many cases the existence of the disease may be suspected from some of these general manifestations without minute or special examination of the stomach, and it is important to recognize these general features, especially in cases in which the degree of enlargement is such that doubt may arise as to the real existence of dilatation, or in which the motor function cannot be properly estimated or is not greatly disturbed.

We take up the diagnostic features of the disease in the usual order of physical examinations.

Inspection. The patient usually presents more or less characteristic general appearances. He is emaciated, often cadaverous in appearance; the skin is dry and harsh and may be unnaturally wrinkled; after a time the epidermis becomes thickened and may form hardened scales upon the surface. The cutaneous circulation, particularly in the extremities, is sluggish, and coldness and blueness of the hands

and feet are commonly observed. The patient's expression is apathetic and the facies are characterized by a peculiar haggardness.

The abdominal examination frequently reveals abnormal distention. This may be seen in the left hypochondriac or the umbilical regions, but more frequently the upper part of the abdomen is hollow and depressed in a transverse furrow, while the hypogastric region is greatly distended. In advanced cases the hollowness of the epigastric region in contrast with the lower portions of the belly is a striking and significant fact. Not rarely peristaltic waves may be seen passing from left to right over the distended stomach, and occasionally reversed peristalsis or antiperistalsis may traverse the swelling from right to left. The veins of the lower portion of the abdomen, particularly those passing upward over the iliac fossæ, are habitually enlarged and prominent.

Palpation. In cases in which the abdominal walls are lax it may be possible to feel the lower margin of the greater curvature throughout a considerable portion of its extent through the abdominal walls; and when the organ contains a certain amount of water it may be possible to produce a succussion splash palpable to the examining hand. More commonly no definite outline is palpable, but the peristaltic waves before referred to may be felt passing to and fro. Palpation is frequently of service in differential diagnosis in determining the existence of pyloric thickening or new growths.

Auscultation. Auscultation over the stomach frequently demonstrates signs indicative of the passage of liquid from the œsophagus into the stomach. The significance of these sounds, however, remains more or less doubtful, and they are of no practical service in the diagnosis of dilatation. Of some importance are the succussion sounds heard when the stomach contains a certain amount of liquid and air. In themselves these sounds are of no special significance, since they are discovered in stomachs presumably healthy. When, however, they occur at times at which the stomach should normally be entirely free of liquid contents, their significance at once becomes apparent in indicating loss of motor function and abnormal retention of the gastric contents. These succussion sounds vary very greatly in intensity, and certainly in the normal stomach never become distinct enough to be plainly audible at a distance, while in gastric dilatation we have repeatedly found them so distinct that they could be

demonstrated to students standing about. Besides the succussion splash another auscultatory phenomenon deserves mention, namely, the loud gurgling or rumbling sounds occasionally heard. Patients are frequently able to develop these when standing upright, and their significance is open to considerable question. For ourselves we have always felt that the existence of these sounds was indicative of gastric or intestinal relaxation, though it must be confessed that they are heard in cases in which dilatation could scarcely be supposed to exist.

The splashing sounds referred to before may easily be simulated by sounds originating in the transverse colon or in other parts of the intestines and resulting from the presence of gas and liquid within these viscera. In cases of doubt, therefore, the colon should be carefully freed of its contents before the test is applied.

Of late the attempt has been made to determine the existence of atony or of dilatation of the stomach by the amount of liquid necessary to produce splashing sounds. This test, however, in common with others which we shall have occasion to allude to, lacks precision and significance, principally because of the varying capacity of the stomach in different individuals, and because of the danger of mistaking dislocation of the organ for dilatation.

We shall refer again to auscultation in connection with percussion in describing the method of auscultatory percussion.

Percussion. The determination of the outline of the stomach by percussion is open to a number of fallacies, and deductions cannot properly be drawn on account of the varying anatomical conditions. Neither the relations of the various borders of the stomach to the different bony points of the thorax nor the actual measure of gastric tympany obtained in transverse, vertical, or other directions are reliable on account of the differences in structure and contour of the thorax in different persons, on the one hand, and on account of the very wide variation in the size of the stomach in presumably healthy individuals, on the other hand. In so far as the value of percussion itself is concerned, it must be recognized that the amount of distention, the quantity of material contained within the stomach, and the condition and position of adjacent viscera must largely influence the results. In particular, the position of the lower border is difficult to determine from the fact that the tympany obtained over the transverse colon may so closely resemble that obtained over the stomach

that an accurate separation of the two is impossible. In the second place, not rarely the colon overrides the stomach and thus makes the determination of the lower border of gastric tympany impracticable. When the left lobe of the liver is enlarged or unnaturally prominent in the epigastrium, it is difficult or impossible to determine the exact outlines of the stomach even though it be quite well distended. To a certain extent percussion may be rendered more precise and valuable by cleansing the colon carefully, and by repeating the percussion in different positions, but despite these precautions no reliable deductions can be drawn.

Other Methods of Determining the Size and Capacity of the Stomach. Perhaps the oldest method devised for this purpose is that of Leube of introducing a stiff sound and palpating the end through the abdominal walls. The dangers and unreliability of this method have, however, led its originator himself to abandon it, and the method is no longer practised anywhere.

A variety of methods have since been introduced which, for the most part, depend upon the amount of liquid that may be introduced into the organ. These, however, are all subject to objections of a serious character. The tolerance of the patient varies so greatly that one will complain of pain when the stomach is scarcely at all distended, while another will bear the greatest possible amount to be introduced. This objection alone would suffice to make these methods unreliable were there not the greater difficulty—that stomachs vary widely in their capacity in different individuals of the same age, size, etc. We therefore place no reliance at all in these methods excepting so far as it may be assumed with tolerable certainty that a stomach which will accommodate 2.5 or 3 litres is probably larger than normal. The usual standard that has been adopted is 1700 c.cm., but this is certainly too small to warrant positive deductions.

In another group of methods the attempt is made to localize the lower border of the organ, and of these that which has attracted most attention is the method of Dehio. This observer, it will be recalled, determines the lower border by introducing measured quantities of water into the stomach and determining the lower border by percussion, the patient standing erect. He has determined that the lower border will be found 11.5 cm. below the end of the sternum after the introduction of one-quarter litre of water, and that the border descends between

2 and 3 cm. with each additional quarter litre introduced; but that in the normal individual the lower border never descends below the umbilicus. With this last conclusion we are quite ready to agree, though we cannot regard the method free of objections or its results valuable in the diagnosis of dilatation. Our own studies with other methods lead us to entirely the same conclusion regarding the lower border, viz., that it always lies above the umbilicus. When, however, it is found below the umbilicus the conclusion is by no means warranted that the stomach is dilated. The same thing will be found in dislocated stomachs, and this condition, we are convinced, is one of great frequency. The method itself is open to some objections which impair its entire reliability, but on the whole it is useful for the determination of the lower border of the organ. The great weakness of Dehio's plan, or rather the great error of many of those who have used it, is the interpretation that has been placed upon the results. We still employ the method and find it satisfactory; but in all cases we seek to control the result by auscultatory percussion and by inflation, and in particular to determine the position of the lesser curvature and of the pylorus. If, then, by Dehio's method we find the lower border of the organ below the umbilicus and the pylorus and lesser curvature similarly depressed, we conclude that dislocation or vertical position is the cause of the depression of the lower border rather than dilatation.

Finally, we would add a few words regarding the method of illumination. This, we must confess, has not from the first appealed to us as a practical method, though in hospital practice it seemed to offer the hope of accurate and useful results. Our own experience is very limited and not very encouraging; and if the results of Martius and Meltzing indicate the conclusions as to the normal situation of the stomach and are to be attributed to the method and not to their having investigated cases of gastroptosis, we are disposed to believe that gastro-diaphanoscopy will not prove a reliable guide. Certainly the method of inflation, which can scarcely give erroneous results when it is at all successfully practised, and the experience of post-mortem examination do not warrant the belief that the stomach normally occupies a position so far down in the abdomen as Martius and Meltzing have found. It seems likely to us that the light radiates through adjacent coils of intestine and thus gives rise to false impressions.

There remain two methods of examination, the value of which we have tested in many cases and of which we feel fully convinced.

Auscultatory Percussion. For some time past we have practised this method in view of the unreliability of simple percussion. Auscultatory percussion, though by no means an original or novel method of examination, has not, we believe, received the attention it deserves nor has its reliability been sufficiently investigated. In our own experience with this method, not only in the examination of the stomach, but also of the heart, the liver, and other solid viscera, we have become convinced that its results are far more accurate than those of ordinary percussion, and that, so far as the stomach is concerned, it may be depended upon to furnish a reliable indication of the position, and to a certain extent of the size, of the organ under the conditions present at the time of the examination. Of course, it is open to some of the objections which may be urged against ordinary percussion, namely, that the distended colon may cover over the inferior border of the stomach, and that the results must vary according to the degree of distinction of the stomach itself. It is not, however, liable to the error that the left lobe of the liver may obscure the gastric tympany, as the note is readily transmitted through this to the stethoscope. In applying the method to the examination of the stomach we use a double stethoscope with long rubber conductors, so that while the patient supports the bell first near the position of the fundus, then below and toward the body or pyloric end, the observer is able without discomfort to perform the percussion, approaching the stomach gradually from all points. Next the percussion is reversed, the finger or pleximeter being placed over the stomach itself and near the bell of the stethoscope; then gradually carried outward toward the periphery until the limits of the organ are passed.

In this manner it is extremely easy to determine the exact limits as far as the method permits of accuracy, and we have repeatedly found that several persons practising auscultatory percussion at the same time have obtained limits which did not vary above ½ or 1 cm. Furthermore, in cases in which we have practised this method and in which subsequently inflation with atmospheric air was used, or in which the accuracy of the determination was controlled by post-mortem examination, we have found that the outlines of the stomach, as determined by the auscultatory percussion, have been extremely

reliable. In normal individuals the position of the fundus, of the lesser curvature, of the lower border, and of the pylorus, have generally corresponded with the outlines given by Luschka, while in cases of dilatation and in cases of gastroptosis wide variations from the normal position or size have been readily demonstrated.

Inflation. Far more useful, however, than any of the methods thus far described is that of inflation. A number of methods have been proposed, the best known of which is that performed by administering bicarbonate of soda followed by tartaric acid. Our experience with this method is comparatively limited, as the objections which have been urged against it and which have occurred to us have made us hesitate to employ it, except in occasional instances, and, further, because we have found the method of inflation with atmospheric air entirely satisfactory. The administration of effervescing mixtures seems to us objectionable from the fact that the distention is entirely uncontrollable, and that in cases of ulceration or other disease of the stomach dangerous results might follow. Thus we have known of cases in which considerable irritation was produced, and others have been reported in which actual hemorrhage was caused. The method is unreliable also in that at times the amount of gas generated falls short of that necessary for distention of the stomach. Still further, it may be objected that sudden and intense distention may give rise to serious pressure or reflex disturbances, though no actual cases proving this suspicion are known to us. On the other hand, the method of inflation with atmospheric air has the one objection, that it necessitates the passage of a stomach-tube, but this is certainly an objection of little importance. There are, of course, certain cases in neurotic or over-sensitive individuals in which the passage of a tube may be objectionable; but where the necessity of making an accurate diagnosis of a possibly serious gastric disease arises, objection to the passage of a stomach-tube is certainly scarcely worth consideration, and, as accurate diagnosis will require the passage of the tube for other purposes, it is not likely that this objection will interfere with the application of the method. For the purpose of inflation we employ a simple bulb, such as that used in the ordinary Davidson syringe, and begin the inflation by vigorous and rapid compressions, so that the amount of air projected into the stomach at the beginning may be as considerable as possible. In this way it has seemed to us

that the pylorus is at once placed in a condition of spasm or contraction, and that thus the escape of the air into the intestine is prevented. The latter accident, however, does sometimes occur in cases of relaxation of the pylorus, but more frequently some of the air tends to escape along the œsophageal tube. The stomach is soon filled and becomes plainly visible through the abdominal walls, so that its size, its outline, its position, and, most important of all, the position of the upper curvature, the pylorus, and the inferior border are readily made out. We have employed this method in numbers of cases of gastric dilatation and other conditions, and have come to regard it as the only satisfactory means of determining the size and position of the stomach.

We proceed now to the second point of importance in the diagnosis of gastric dilatation: to the determination of the motor activity or sufficiency of the walls of the stomach. Here, too, we find a number of methods recommended. Among the older of these is the salol test, to determine the duration necessary for propulsion of the contents into the duodenum, the assumption being made that the decomposition of the salol speedily follows its entrance into the alkaline intestinal secretions. According to Ewald, this takes place and the resulting salicylic acid appears in the urine within forty to sixty minutes, in health, and not until a much later period in gastrectasis. It is unnecessary to enter upon the discussion of the merits of this test. Numerous observers have found and our own experiences have taught us that Ewald's method possesses no practical usefulness.

Another plan proposed was that of introducing a measured quantity of oil into the stomach and removing the portion remaining after two hours with the stomach-tube. This method has the great disadvantage that complete removal of liquids from the stomach is often impossible, and that the limits of normal motor activity probably vary more widely than such a test would permit us to believe.

The most reliable method of direct determination of motor insufficiency is that of v. Leube. According to this observer, all traces of a meal of meat, soup, and bread disappear from the stomach in the course of seven hours, when the motor activity is normal. When atony is present food remnants may be found at much longer intervals after the meal; and even on the morning of the next day, when the test-dinner was given in the evening. This method is easily practised,

and, in view of the wide variations which doubtless exist in different individuals, is as accurate as we may expect.

The elaborate methods of measuring and recording motor activity with the aid of instruments, acted upon by columns of water or air compressed in bulbs or other contrivances introduced into the stomach, are cumbersome, impracticable, and therefore useless. It is therefore unnecessary to consider their sources of error.

Dehio has claimed that his method of determining the lower border of the stomach by introducing measured quantities of water is useful also for the estimation of motor activity. He has found that in cases of atony the lower border of the stomach descends to the umbilicus with the addition of only moderate quantities of liquid, while the border in dilatation is found below the umbilicus even after the introduction of the first quantity. From such differences in different cases he would determine the less or greater motor power. This assumption, however, seems to us an unwarranted one, and we agree with Riegel in his assertion that greater elasticity does not of necessity imply less motor power; but entirely aside from this point, the method of Dehio is fallacious, in that it does not take into consideration movability of the stomach apart from dilatability.

In addition to these methods of determining the motor power directly, there are certain examinations, particularly the chemical investigation of the gastric contents, which furnish evidence of the delay of food in the stomach. The most striking and obvious feature is the decomposition which leads to sour and ill-smelling vomita. To a certain extent this is a measure of the motor insufficiency, as is also the presence or absence of sarcinæ, yeast fungi, and other organisms of fermentation and putrefaction. In cases of extreme delay of the contents of the stomach, decomposition of the starchy and saccharine foods may lead to the formation of lactic, acetic, butyric, or other fatty acids, while putrefactive changes of proteids lead to ill-smelling gases containing sulphuretted hydrogen in particular. The existence of these substances in vomited matters or in the stomach contents removed with the tube is always indicative of undue retention of the food. The amount and kind of decomposition that prevails depends to a large extent upon the kind of food taken and the character of the gastric secretion, especially upon the presence or absence of free hydrochloric acid. Boas has recently maintained that the presence

of lactic acid in the stomach contents after a test-meal containing no lactic acid is specially significant of carcinoma. This point is in a measure established, though it has not the pathognomonic importance Boas sought to give it. Lactic acid is occasionally found in non-malignant cases, as in one case of our present series. On the other hand, repeated examination may fail to show it in cases of carcinoma, as we have found. We need not enter more fully upon this controversy now. Suffice it to say that lactic acid when present is an indication of stagnation.

The amount of urine is another indirect evidence of motor insufficiency. Von Mering's investigations and the subsequent clinical observations of many others have shown that the mucous membrane of the stomach plays little part in absorption, either of liquid or of other matters. In consequence, obstruction of the pylorus and vomiting lead to rapid desiccation of the tissues and to decrease in the quantity of the urine. This decrease, however, is largely dependent upon associated conditions, and may fluctuate considerably, so that the exact quantity is of little value in diagnosis or in determining the degree or progress of the disease.

We have thus sketched the principal methods of investigation and points in the symptomatology which are of value in the determination of gastric dilatation. Of necessity, allusion has been made to certain methods which we do not ourselves employ, and of whose value and reliability there may be much question. The methods upon which we rely are those of auscultatory percussion and inflation, and upon Dehio's method for determining the lower border of the organ. The mere determination of one or another of the borders of the stomach is of little value, but taken in connection with the other portions as determined by the same or supplementary methods of investigation, and with the discovery of deficient motor activity, the diagnosis can generally be made with ease. Mistaken diagnoses are more often the result of insufficient examination than of unreliability of methods at hand.

Differential Diagnosis. The points upon which this will rest have been more or less thoroughly considered, but it seems advisable to point out certain contrasted conditions with the indications pointing to one or the other; and to consider somewhat the methods by which an opinion may be formed as to the original cause.

Megalogastria and Gastrectasia. Ewald, Riegel, and others have described cases of enlargement of the stomach without symptoms of functional disturbance. Such cases are doubtless instances of physiological or natural largeness of the stomach, and may properly be designated as megastria or megalogastria. What we have before said regarding the variation in the size of the stomach in different persons need not be repeated, but it is clear that no definite limits can be assigned to what may be considered a normal stomach. How large a stomach may be without danger of stagnation of food on account of the mere capaciousness is difficult to say, and cases of enlargement sufficient to be certainly recognized by clinical methods, and in which no symptoms of dilatation are found, are comparatively rare. The diagnosis is simple enough, and depends altogether upon the fact that no signs of stagnation of food or of serious disturbance of digestion can be discovered. The only difficulty offered is to distinguish cases of obstructive enlargement with compensatory hypertrophy of the walls of the stomach. In the latter, however, there is always a history of gastric disease running backward for varying periods; and usually, if not always, the compensation is only partial, some deficiency of motor activity being present. The general appearance of the patient also gives important indications, and in cases of non-malignant pyloric stenosis there is usually excessive acidity of the gastric secretion, and subjective symptoms more or less severe.

Gastroptosis and Gastrectasia. Displacement of the stomach —the vertical position of Kussmaul or gastroptosis of Glénard—has long been recognized, but its frequency has been underestimated, and without doubt it has often been mistaken for gastrectasia. A consideration of the anatomy and relations of the stomach is convincing of the fact that displacement must affect the pyloric end almost entirely, while the cardiac end and fundus are more or less normally situated. The result of displacement, therefore, is a vertical position such as occurs in the newborn. In normal individuals, after early infancy, the position of Luschka is assumed and retained; but very often, as a result of the pressure of clothing about the waist or of other causes, displacement occurs and causes the pyloric end to fall to lower levels than normal. The frequency of such a pathological position is probably greater than has been generally believed, and in our experience with inflation of the stomach we have found it surprisingly frequent.

In gastrectasia the pylorus usually also descends somewhat, though rarely so much as in gastroptosis. When studied in relation with the lower border the position of the pylorus is found relatively little displaced. Dilatation habitually affects the greater curvature near the pyloric end more than other parts,[1] and in consequence the distance between the pylorus and the lower border becomes excessive. This is very well seen in some of our diagrams (Figs. 2, 3, and 4) as well as in illustrations given by various authors.

These considerations show the value and necessity of determining the position of the pylorus and lesser curvature as well as that of the lower border, and the unreliability of basing deductions upon Dehio's method alone. If the pylorus is not much displaced and the lower border is below the umbilicus, dilatation probably exists; but if the pylorus is near the umbilicus, the low position of the lower border loses its significance. In certain cases of gastroptosis a moderate amount of associated dilatation may exist. In such cases the diagnosis, as far as the mere estimation of size is concerned, depends upon our judgment as to whether the descent of the lower border is out of proportion to that of the pylorus and lesser curvature or not. The absolute diagnosis, however, in such cases depends upon the determination of the motor activity of the walls.

Obstructive and Atonic Gastrectasia. The differential diagnosis between these conditions may be extremely difficult in some cases, particularly when the early history is wanting. Where a distinct neoplasm is discoverable the diagnosis becomes a simple one, but in the absence of this it must depend upon a consideration of the course of the disease, and to a certain extent upon the degree. Very rarely does atonic dilatation reach the enormous grades sometimes witnessed in obstructive gastrectasia. In addition, it will be found that the course of the case is less regular and progressive. Not rarely there will be a history of early remissions and accessions in the disturbances, and when the patient is continuously under observation marked variations may be noted from time to time. Physical examination is less apt to discover peristaltic waves, and the chemical examination shows no such marked excess of HCl as is seen in many cases of non-

[1] Certain investigators have found that the portions of the stomach near the pylorus are especially active in expelling the contents. It is clear, therefore, that those parts would suffer most distention in cases of obstructive dilatation. In any event, however, the most dependent part of the organ would be prone to dilate.

malignant stenosis. It must be admitted, however, that some cases of dilatation beginning with hyperacidity and hypersecretion are atonic rather than obstructive. Obstructive dilatation differs in its course mainly in that it is progressive and persistent. The earlier stages, during which compensation is maintained, may be marked by few symptoms; but after compensation fails, and often this occurs quite as abruptly as failure of compensation in cardiac disease, the disease is lasting and quite regular in its downward course. The dilatation in this stage often reaches proportions never attained in atonic cases.

Malignant and Non-malignant Obstructive Gastrectasia. The general appearance of the patient gives us less information than we might expect. Not rarely, as has been already noted, the patient assumes a cadaverous, cachectic appearance in entirely non-malignant dilatation, while, on the other hand, instances may be found of cancerous obstruction in which the general appearance of the patient is quite good. The investigation by physical examination, and particularly the chemical examination, may furnish important diagnostic factors. The most significant fact is the discovery of excess of HCl in certain non-malignant cases. The mere presence of hydrochloric acid, even in a case of excessive obstruction with dilatation, does not exclude carcinoma, as we have several times found; but excessive hydrochloric acid does not seem ever to occur in such cases.

The presence or absence of lactic acid has been urged by Boas as a fact of diagnostic value. This, however, requires further confirmation. Boas himself admits the occasional presence of small quantities in non-malignant dilatation, and one of our present series of cases showed the same. On the other hand, lactic acid may be absent in cases of cancer, as we have also found. On the whole, however, it seems fairly well established that the occurrence of lactic acid (when sought after according to Boas's method) is a point of considerable value as indicating carcinoma. Further, it has been held by Boas that albuminous decomposition with production of sulphuretted hydrogen occurs in benign rather than in malignant cases, but we have found it present in both forms.

The discovery of a palpable tumor in the pyloric region is the most suggestive fact of all, and usually serves to establish a positive diagnosis. At the same time it must be remembered that hypertrophic thickening of the pylorus may simulate carcinomatous tumors, and

that enlarged lymphatic glands and even the head of the pancreas may be felt and mistaken for carcinoma. Recently examination of the blood has been suggested as a means of making a differential diagnosis, the studies of R. Müller and Schneyer showing that digestive leukocytosis is wanting in carcinomatous stenosis but normal in foreign cases. Finally, the rapid progress of the case, occurring in a person beyond the age of forty, and without a history of prolonged gastric troubles, adds to the probability of the cancerous nature of the obstruction.

CASE I. *Obstructive dilatation; non-malignant stenosis of the pylorus.*—C. M., aged thirty-five years, a laborer, was admitted to the hospital December 7, 1895. His father had died at the age of forty-five years, the cause not known. His mother and four sisters are living and in good health. One sister died of pneumonia. Nothing in his family history bears on his present case.

He himself was a healthy lad until about his twentieth year, when he had a vague attack of malarial fever and was confined to bed for three weeks. In 1883 he was injured in a coal mine, and in 1884 was again injured. In 1890, while working in an iron mill, he was overheated and afterward chilled. This led to an illness which was called hepatitis and which confined him to bed for fifteen weeks. There were chilliness, vomiting, and a great deal of pain, the latter referred to a point on the right side between the anterior superior spine of the ilium and the umbilicus. The patient has always been a temperate man with regard to the use of alcoholics and chewed tobacco only moderately. He was careful in his manner of eating, generally taking his food regularly and chewing it well.

The illness which brought him to the hospital was gradual in onset and had been increasing during the past two years. He first noticed eructations of gas and then began to suffer with a heavy feeling in the stomach, relieved by vomiting. The latter did not begin until some time after the first symptoms, but became constant after their onset.

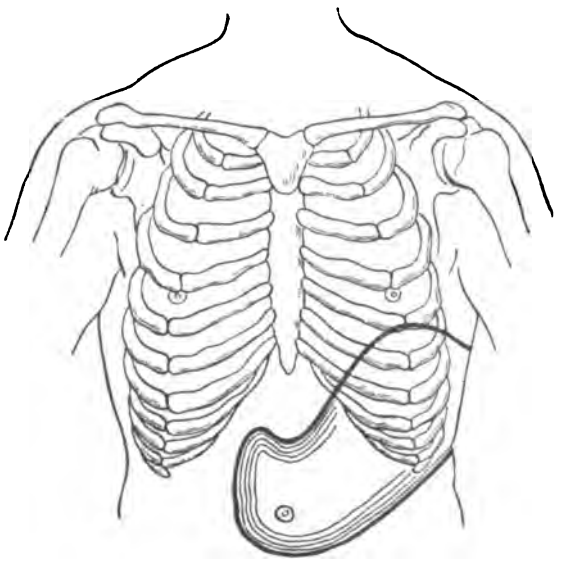
Physical examination. When the patient presented himself he was considerably emaciated, the malar bones standing out prominently. His voice was rather hoarse, his skin dry and scaly, and in general there was a desiccated appearance. On examination, it was found that the upper part of the abdomen (epigastrium) was rather hollow, while the lower part (below the umbilicus) was greatly enlarged. The superficial veins, especially those on the lower and lateral portions of the abdomen, were much enlarged. The size of the stomach was determined by auscultatory percussion and found to be unusually large. Splashing sounds were evident when the fingers were pressed against the abdominal wall as well as on shaking the patient. The contents were removed with the stomach-tube and were found to consist of 2500 c.cm. of horribly offensive decomposed material. Chemical analysis of this showed a total acidity of 67, with a considerable proportion of free HCl (40 by Braun's method for free and combined HCl), and lactic acid in considerable quantity (Uffelmann's test).

The patient's blood was examined, showing 3,863,000 red corpuscles and 9300 white corpuscles. The urine showed as follows: volume for twenty-four hours, 1718 c.cm.; turbid and yellowish; reaction slightly alkaline; specific gravity 1020; no albumin; no sugar; P_2O_5, 3.126 g. (0.182 per cent.).

The patient was ordered lavage and a graduated albuminous diet, with a restriction of liquids, electrical stimulation, and high colonic douches. Under this treatment his general condition improved somewhat, though the condition of the stomach remained about the same.

It was constantly found that the food of the previous day could be removed from the stomach in the morning, and sometimes portions of food from several days previous were thus obtained. There was constantly excessive acidity, and free hydrochloric acid was invariably found present, the quantity ranging from 30 to 56. Lactic acid was occasionally present to Uffelmann's test, but was never detected by Boas's method, though repeatedly sought for.

FIG. 2.



The size of the organ was evidently greatly in excess of the normal, and in practising lavage it was found that from 2½ to 3 litres caused no particular discomfort. Auscultatory percussion found that the organ extended from its usual position beneath the left lung and heart downward as far as the umbilicus and even further, and that the pylorus, though somewhat depressed, was separated from the lower border by a considerable space. Inflation with air gave a similar result, and the organ was readily demonstrable to a class of students in an amphitheatre.

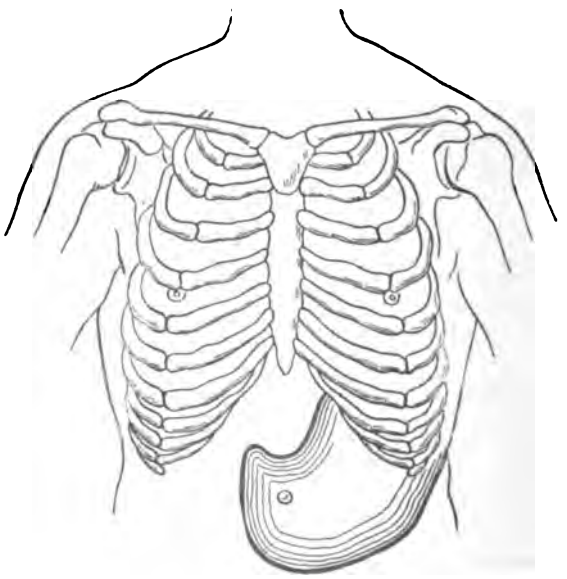
The patient's general condition improved somewhat, but he continued to have burning pain, heaviness, disturbances of sleep, and attacks of vomiting. It was finally decided to operate. Dr. J. William White was called in and performed the operation of divulsion, finding the obstruction at the pylorus due to a circular ring of dense sclerotic tissue, which at first sight presented the appearances and feeling of a carcinoma.

The subsequent history of the case was eminently satisfactory, the recovery from the operation being prompt and the restoration of the stomach to its normal functions almost complete.

Lavage has been practised on two mornings and no food remnants of the previous day obtained. A Boas's test-meal was found to have passed into the intestine after two hours.

CASE II. *Obstructive dilatation; carcinoma of the pylorus.*—C. L. P. was seen with Dr. Lee H. Smith, of Buffalo. The patient, a banker, aged fifty-four years, was treated twice in 1887, being operated upon for stricture of the urethra the latter time. A cure of this disease was effected, and there does

FIG. 3.



not appear to have been any recurrence of the trouble. His general health since then continued to be very good until September, 1895, when he noted obstinate constipation—not relieved by usual exercise and diet. He never had any severe illness which confined him to his bed, but has always been bilious at times. Within two months of his death he began to lose weight very rapidly, and in five months the loss amounted to thirty pounds. Within

the last three or four weeks of his life he vomited a few times. His digestion became very poor. Frequently his food gave distress, and sour, windy risings from the stomach were distressing. Bowels inclined to be constipated; no jaundice. He suffered with piles, especially when the bowels were constipated. The lungs and heart were examined with negative results, excepting slight cardiac debility. His general circulation was weak, due to anæmia. When the patient came under our notice the above symptoms and history were obtained from Dr. Smith, and in addition we made careful examination of his abdomen and stomach. There was extreme emaciation, and the skin presented an ashy hue. The abdomen was depressed above (hypochondriac and epigastric regions) and distended in its lower portions. A small tumor could be felt in the right side above the umbilicus, and on auscultatory percussion the size of the organ was found to be enormous. Splashing sounds were very evident. Inflation was practised, and the stomach was found to occupy the position represented in the accompanying diagram.

Repeated examinations of the gastric contents had been made and the total acidity was habitually decreased; free hydrochloric acid was never discovered. Lactic and butyric acids were occasionally present, but it is not stated that special precautions were taken to exclude lactates from the test-meals. Pepton was often found. Sarcinæ were seen microscopically; but no cancer-cells or acini.

The urine was high-colored and heavy (1028), contained excess of indoxyl, sulphuric acid, and a trace of albumin with fine granular casts.

The diagnosis of dilatation due to carcinoma of the pylorus was easily arrived at, and was subsequently confirmed by an operation performed by Drs. J. William White and W. W. Keen.

CASE III. *Obstructive (?) dilatation; movable kidney.*—Miss M. P., aged twenty-nine years, a type-writer by occupation, was admitted to the hospital December 10, 1893. Her father was killed in an accident; her mother was still living and had an aneurism of the aorta. She had had the usual infectious diseases of childhood, and especially diphtheria, which she had three times. In November of 1891 she had typhoid fever. The following notes were recorded:

Her present illness seemed to begin in June of 1892, when she first began to suffer with pain in the left hypochondriac region and with flatulence. The ingestion of food was followed by burning pain and by heaviness, but there was no vomiting. Previous to this time she had suffered with no disturbances of the appetite or digestion, and her bowels had been entirely regular. In July of 1892 she was thrown from a carriage and severely bruised. From this time the symptoms continued and gradually grew worse until March, 1893, when vomiting commenced. The matters vomited were dark in color and always extremely sour. At first this occurred at long intervals, but finally during the summer it was sometimes repeated several times a day. The patient became very much wasted and constipation grew progressively more intense. There were no menstrual periods after August,

1893. She complained of continuous pain and sometimes of sharp paroxysmal attacks.

Physical examination. The patient was emaciated and the abdomen rather flat. During the examination, however, a distention appeared below the border of the left ribs, constituting a veritable phantom-tumor. The percussion note over this was low-pitched and tympanitic. Peristaltic waves were plainly visible, and on shaking the patient a succussion splash was quite audible. The distention appeared and disappeared rather rapidly during the time she was under examination. The lower part of the abdomen was somewhat fuller than the upper. In the right hypochondriac region and toward the umbilical region there was found a hard, kidney-shaped tumor which was painful on pressure and easily movable. The condition of the other abdominal organs and the thoracic viscera seemed normal.

The patient was ordered repeated rectal enemata, but diarrhœa set in and the treatment was discontinued. For some time the condition remained the same, and from time to time she had attacks of vomiting, the matters discharged frequently being remnants from the previous day.

Examination of the gastric contents, after an Ewald test-meal, showed diminished acidity (10 to 20 NaHO); no hydrochloric acid; lactic acid present (Uffelmann's test).

Careful regulation of the diet, for the most part peptonized milk; rest in bed; Faradization over the stomach and back; cod-liver oil, given by the mouth or by inunction; and occasional intestinal lavage, constituted the treatment. Her condition gradually improved, and in the course of four months she had gained thirty pounds. The kidney-shaped tumor, which had been plainly palpable during the first two months, had gradually receeded until it was no longer palpable, and the stomach on physical examination (by auscultatory percussion) was found to occupy its usual position and had seemingly the normal size.

The patient returned somewhat later, reporting that she had resumed her usual occupation, and she was found to be in excellent health, having suffered no further discomfort from indigestion, vomiting, or pain.

In this case inflation of the stomach was not practised, and the diagnosis of dilatation therefore rested upon the determination of marked failure in the motor power by the discovery of food-remnants in the fasting stomach, upon the apparent enlargement obtained by auscultatory percussion, together with the active peristaltic waves visible through the abdominal walls, and finally the subsequent disappearance of all of these conditions.

CASE IV. *Atonic and obstructive dilatation, due to a cicatrix in the anterior wall and adhesions surrounding the pylorus.*—P. D., aged fifty years, a shoemaker by occupation, was admitted to the hospital January 3, 1896. The following notes were recorded:

The family history of the patient does not bear upon his illness. The patient was married and has five healthy children.

He was a healthy man excepting for an attack of malaria, which he had ten years ago. He has used alcohol very little and tobacco not at all. He has always been careless in his habits of eating, bolting his food with insufficient mastication. His appetite has always been good and he has habitually eaten large quantities of food.

About five years ago he had some trouble with his stomach, but no severe discomfort. Eructation of gases was the most pronounced symptom, and occasionally at long intervals he would vomit.

About a year and a half ago there was a severe spell, coming with a chill and accompanied by fever and vomiting, which confined him to bed for three months. The stomach was absolutely unretentive. He finally recovered and returned to his work. Six months or a year later, however, he was seized with the same sort of an attack and was confined to bed for four months. During the attacks he lost much flesh, but on recovering again gained weight.

The summer after the last attack he felt as well as ever, but continued his habits of rapid eating, and about September, 1895, the present condition began.

The first symptoms were marked eructations of gases, heartburn, and continuous pain in the epigastrium. The latter was relieved by eating, but this food was not digested and invariably was vomited after several hours in an undigested condition. Sometimes he has vomited enormous quantities of sour, watery, and yeasty matters, but has never noticed blood. His bowels are very costive and the quantity of urine is diminished. Now and then he complains of an aching pain running down the limbs.

Physical examination. The patient has an elongated frame. The lower part of the chest and the end of the sternum are depressed, as are also the epigastric and hypochondriac regions; whereas the hypogastric and lower umbilical portions are distended, and the superficial veins along the sides and front of the abdomen are enlarged.

The stomach was outlined by auscultatory percussion and was found to measure 17.5 cm. in a vertical direction and 22 cm. in the transverse direction. The lower border is on a line with the umbilicus; the upper border lies beneath the fifth rib. (The outlines are illustrated by the accompanying chart.)

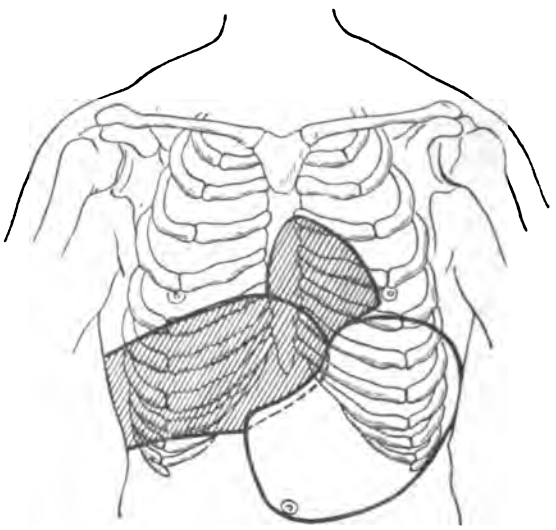
The cardiac outline is not increased and the liver is apparently normal in size. Careful palpation reveals no evidence of a tumor, but in the epigastric region toward the left costal border there is felt a distinct resistance.

The contents of the stomach were removed with the stomach-tube, and were found to consist of decomposed, sour, ill-smelling liquid. Chemical examination of this showed excessive acidity, varying from 30 to 120 on different occasions. There was always free hydrochloric acid, the amount of the latter varying from 10 to 50. Lactic acid was frequently present to

Uffelmann's test; and on two occasions, when Boas's test-meal was given and all other precautions were taken, the reaction was still positive.

The stomach was emptied at varying periods after meals, and always contained food-remnants; and not rarely vomiting would bring up food taken on the previous day. The amount of liquid discharged by vomiting was often very great (2500 to 3500 cc.).

FIG. 4.



The urine was usually a little turbid, alkaline in reaction, and varying in its specific gravity from 1015 to 1020. No albumin nor sugar, but excessive deposits of alkaline salts (phosphates and carbonates). Indican was found in excess.

The patient was placed upon carefully regulated diet of albuminous character. Lavage of the stomach and cold douches of the colon were given at regular intervals, and at times nutritive enemata were ordered. No improvement occurred, and operation was decided upon. This was performed by Dr. J. William White. On incision, the stomach was found enormously enlarged, and a dense scar was found in the anterior wall, at the point where the feeling of induration had been detected. The serous surface adjacent to this was thickened. The pylorus itself was healthy, but was constricted by fibrous adhesion springing from the head of the pancreas, the posterior wall of the abdomen, and other adjacent parts.

CASE V. *Atonic dilatation; great improvement after six months' treatment.*—P. J. J., aged twenty-five years, was admitted to the hospital October 20, 1893. There was nothing significant in the family history.

The patient began to work in the coal mines at an early age and continued

to do so until two years before he came under observation. Since that time he had been following various pursuits, but for the year previous was almost incapacitated. He had used alcohol habitually and was always an excessive eater; and, as he himself confessed, he "eat enough for two men."

During the last six years he had had occasional attacks of pain in the stomach. This occurred especially at a considerable interval after eating, and was frequently relieved by vomiting of sour liquids. Eructations of gases were frequent. The attacks increased in severity and frequency until they occurred almost after each meal and quite disabled him from work. His appetite continued excessive, excepting at times when the attacks were not relieved by vomiting. At such times the fermentation seemed to continue and the eructations were always more severe and lasting. The bowels are obstinately constipated, and he had pain in the back. Tne tongue was generally clean.

Physical examination. The patient has a long, narrow chest, and the xiphoid cartilage and the lower part of the ribs are depressed, as is also the epigastric region. The abdomen below the umbilicus is much distended. The superficial veins over the latter part are greatly enlarged. Auscultatory percussion discovers a decided increase in the size of the stomach, the pylorus being somewhat depressed, but the lower border extending fully to the umbilicus, which is placed at an abnormal distance from the xiphoid on account of the unusual shape of the patient. Careful palpation of the abdomen reveals no induration or tumor and the intestines appear to be normal. The heart and lungs are healthy.

The stomach-tube was introduced and removed considerable undigested food which had remained in the stomach a number of hours; and in washing out the organ it was found to hold two and one-half litres without difficulty. The stomach-contents contained slight excess of free hydrochloric acid, and lactic acid to Uffelmann's test.

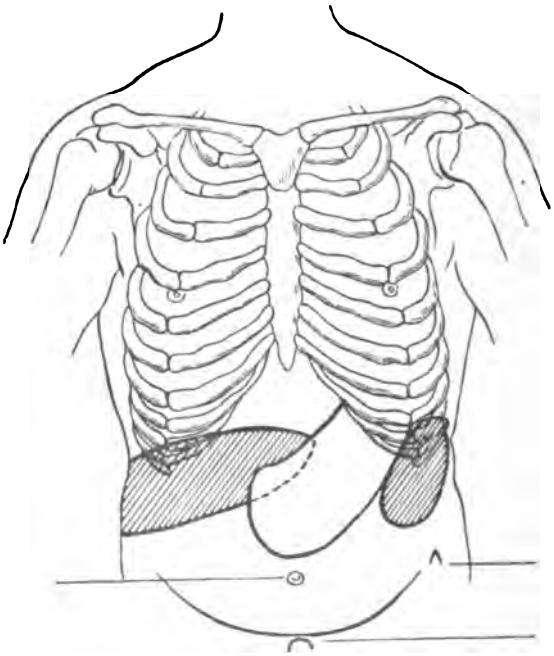
The patient was placed upon a dry albuminous diet and was ordered lavage of the stomach and regular colonic douches. His condition steadily but slowly improved, and after six months he had gained materially in weight and general appearance. The physical examination of the stomach showed that the pylorus had resumed a more natural position, and the lower border had receded considerably from its former position on the level of the umbilicus. Vomiting had almost ceased, and lavage discovered no remnants of food after six hours.

The patient was finally discharged from the hospital, having gained twenty-three pounds in weight and having a comparatively healthy appearance.

CASE VI. *Enteroptosis; displacement of stomach, liver, and spleen; stomach outlined by auscultatory percussion.*—Mrs. B., aged forty-five years; housewife; admitted November 25, 1894. The history obtained was as follows: her father died at the age of eighty-eight years of heart disease; her mother at seventy-seven years of pneumonia. She had two brothers and one sister living and in good health. One brother had died of pneumonia, one of typhoid

fever, and one sister in infancy. She herself had been a healthy child and woman; she had the ordinary diseases of childhood, but not severely. At nineteen she was married, and she had borne nine children. There was one miscarriage at the fifth month. All of her children were large and the labors were difficult. One child weighed sixteen pounds and was delivered with the forceps. The menopause occurred two years ago, since which time she has been growing stout; about the same time she noticed a tumor in the right side of the abdomen. This was moderately painful, and changed its position with different positions of the body. A little later she suffered with pains in the left side, and then noticed a tumor there. When stooping she

FIG. 5.



frequently had sharp pain in the right side, but she has never had any spontaneous paroxysms. She has been moderately jaundiced several times. At times there are shooting pains around the left side, sometimes extending as far as the left arm, and occasionally she has suffered with attacks of palpation. She has had attacks of abdominal colic severe enough to produce semi-collapse; and not rarely, after eating, has a feeling of over-distention. The bowels are occasionally loose. She has kept on with her housework despite her suffering until four weeks ago, when severe pains in her left side and in the left shoulder compelled her to give up. Shortness of breath, which has

always been present to some extent, still persists, and she has a troublesome morning cough.

Physical examination. The patient is a very large woman, the subcutaneous fat being enormously increased but rather flabby. The abdomen is large and pendulous, so that the umbilicus is greatly depressed and the abdominal fold hangs down over the pubes. There is no fluctuation on careful bimanual palpation. The liver is plainly felt on the right side, the lower edge being 15 cm. below the border of the thorax, and the organ is easily movable up and down and laterally. On the left side the spleen is similarly displaced, the lower margin being 9 cm. below the ribs in the anterior axillary line.

Percussion discovers hepatic dulness 2.5 cm. below the edge of the ribs and extending downward 15 cm. and inward as far as the nipple-line. The position and the outline of the stomach were determined by auscultatory percussion. The area of tympany is on a level with the lower margin of the ribs. The lower margin is almost on the line of the anterior superior spines of the ilium. The umbilicus is displaced downward even below this point on account of the pendulous character of the abdomen. Posteriorly no difference could be detected by palpation or percussion of the two renal regions, though there were perhaps less resistance and dulness than normal on both sides.

Examination of the urine showed specific gravity 1030; pale amber color; no albumin; no casts; 1.3 per cent. of sugar. During her stay in the hospital the quantity of urine varied from forty-eight to fifty-eight ounces. Her temperature was about normal. Her pulse and respiration varied slightly from the normal. Examination of the blood showed 4,600,000 red corpuscles, 20,000 white corpuscles, and 60 per cent. hæmoglobin.

CASE VII. *Cancer of pylorus and liver; position of the growth and absence of dilatation determined by auscultatory percussion.*—D. C., aged forty-eight years, miner, was admitted to the hospital February 8, 1896. The patient's health had been good, though he had suffered with a number of lesser ailments. He had used alcohol freely, but was not a daily drinker. He chewed tobacco excessively. He was a rapid eater and habitually bolted his food. There was no venereal history.

When he entered the hospital he asserted that he had been entirely well until three weeks previously, when he was suddenly attacked with a severe pain in the abdomen. This was unaccompanied by vomiting or other symptoms and lasted about two hours. The next night another attack occurred, and subsequently they grew more frequent, coming on several times a day. The pain was generally sharp and cramp-like in character.

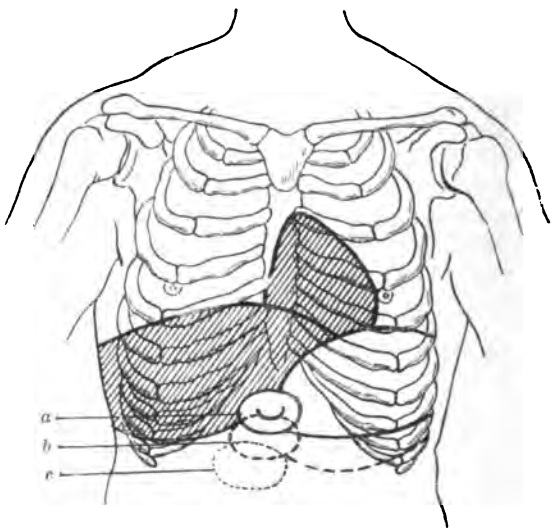
On physical examination there was found a large tumor occupying the mid-epigastric region and seemingly connected with the lower border of the liver. This was somewhat movable with the respirations and could also be moved from side to side.

Auscultatory percussion of the stomach showed that the pyloric end lay posterior to the mass, and the size of the organ seemed rather restricted than

enlarged. With change in position of the patient the position of the tumor and of the stomach tympany was also somewhat displaced.

Examination of the stomach-contents revealed no remnants of food in the morning or at long intervals after eating. The acidity was reduced, varying from 26 to 42. Free hydrochloric acid was repeatedly discovered, the quantity varying from 15 to 20.

FIG. 6.



a. Ordinary position. *b*. Position on full diaphragmatic inspiration. *c*. Position when lying on right side. The last position is somewhat exaggerated in the diagram.

The urine was clear, with a specific gravity of from 1017 to 1025, acid in reaction, and containing some albumin—at times considerable, at other times little. An excessive amount of globulin over serum-albumin was striking. There was no sugar. Hyaline and granular casts and abundant leukocytes were found in the sediment.

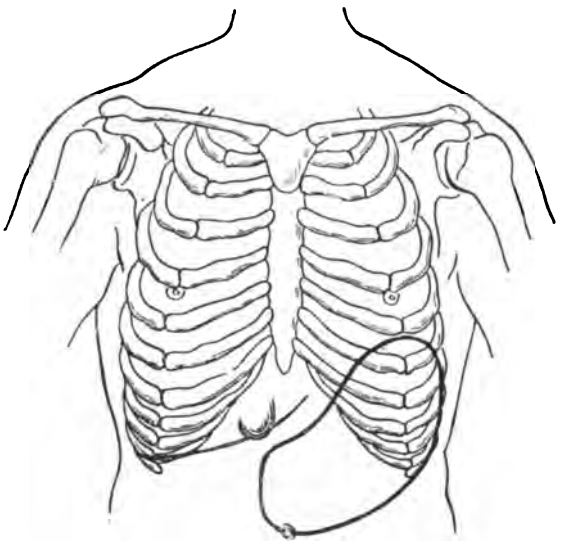
The growth of the mass seemed progressive, and finally it was determined to make an exploratory incision. This discovered that the tumor occupied the position between the border of the liver and the stomach, being attached to both. The stomach itself was not enlarged and occupied the position determined by auscultatory percussion.

CASE VIII. *Tumor of the liver; chronic gastritis; pyloric involvement excluded by auscultatory percussion and inflation; subvertical position of stomach.*—N. C. C., aged sixty-five years, a hotel-keeper, was admitted to the hospital July 18, 1895. He had always been a healthy man, but never worked hard. He used tobacco excessively until two years before, but drank only moderately. He ate very irregularly, and constantly bolted his food without mastication.

In April of 1894 he began to lose weight and suffered with a dry cough. The loss of weight went on steadily until it amounted to fifty pounds. He became weak and sallow in color; his appetite varied, sometimes becoming ravenous. His bowels acted irregularly, but he was rarely constipated. Occasionally he vomited, but lately not at all. There was practically no pain.

Physical examination. The patient is emaciated, sallow, and almost cachectic. The abdomen is rather hollowed, and in the position of the lower border of the liver is seen a distinct, nodular tumor which moves with the respirations. Auscultatory percussion determined that the pylorus lies near the tumor in question or behind it. The liver begins at the fifth interspace and extends 3 cm. below the edge of the ribs. The hepatic dulness is continuous with that of the tumor noted.

FIG. 7.



The stomach-contents were removed after a test-meal, and hydrochloric acid was found present. Subsequently this test was repeated on numerous occasions, and generally there was found a slight amount of hydrochloric acid. Sometimes it was absent. Boas's test-meal was given on three occasions, but lactic acid was always absent. There never was any evidence of retention of food beyond the normal length of time, and the stomach was always empty in the morning before breakfast.

Examination of his blood showed 4,125,000 red corpuscles, 12,500 leukocytes, and 45 per cent. hæmoglobin. The red corpuscles were irregular in shape, but there was no marked abnormality.

The urine was normal in color, acid in reaction, and had a specific gravity of 1018. There was no albumin, no sugar, and no casts.

The stomach was distended with air on several occasions, and it was found to occupy the position seen in the diagram. The lower border was as low as the umbilicus, but the pylorus was also depressed, so that the descent of the lower border was more likely the result of dislocation than of dilatation. When the stomach was inflated it was easy to determine that the mass on the right side was not connected with the pyloric end, as the latter was separated by a distinct and easily determined interval from the tumor in question.

The patient was placed upon a tonic treatment, and was ordered careful diet and remedies directed to the general disturbances of his stomach, supposed to be the result of chronic gastritis.

There was some improvement for a time, but subsequently the condition relapsed. Finally operation was decided upon, and was performed by Dr. J. William White. The mass was found to be a nodular growth in the anterior surface of the liver and projecting also to a certain extent upon the posterior surface. The stomach was uninvolved. No portions of the growth were removed, but the wound was simply reunited. The patient subsequently improved almost without interruption, and when he finally left the hospital, three months later, had gained over twenty-five pounds in weight, and suffered no gastric or other disturbances.

DISCUSSION.

DR. HENRY: Dr. Pepper referred incidentally to the lactic-acid test for cancer, and, therefore, I presume it may be permitted me to mention a method of diagnosis of latent gastric carcinoma, which, of course, may be attended with dilatation. It is a method of diagnosis which I have found of very great value. In cases of latent gastric cancer, as everyone here knows, there is a great simulation of pernicious anæmia, so much so that in many of these cases the diagnosis lies between pernicious anæmia and gastric cancer, and if one or the other can be excluded the diagnosis is made with certainty. The method that I refer to is an examination of the blood for the number of red corpuscles to the cubic millimetre. I have never seen a case of pernicious anæmia proceed to a fatal termination without the number of red corpuscles descending below one million and sometimes as low as three or four hundred thousand per cubic millimetre. I have never seen (and I have seen a good many such cases) a case of carcinoma of the stomach proceed to a fatal termination with any such reduction in the number of red corpuscles per cubic millimetre. I have examined a large number of cases of carcinoma of the stomach in which the diagnosis has been verified at autopsy, and I have found a few days before death between two and three million red corpuscles per cubic millimetre. In other words, as I have phrased it else where, in gastric cancer the reduction in the number of red corpuscles does not keep pace with the cachexia, while in pernicious anæmia, on the other

hand, the cachexia does not keep pace with the reduction in the red corpuscles. As many know, in pernicious anæmia not very long before death, the muscular strength is retained in a surprising degree. In a patient under my care, on whom, perhaps, an autopsy was made to-day or yesterday, with marked signs of stenosis of the cardiac orifice of the stomach, only a few days ago there were between two and three million red blood-corpuscles to the cubic millimetre.[1] On this account I have excluded pernicious anæmia.

I told Dr. Stengel of this fact when he was my resident physician six or seven years ago, and he has frequently confirmed the observation. In a paper which Dr. Stengel published on the pathology of the anæmias he mentioned two cases of gastric cancer in which the number of corpuscles before death was between two and three million per cubic millimetre. Occasionally cases of cancer may be seen in which the number of corpuscles had descended below this point, but in my experience for twenty years in hospital service and private practice I have never seen such a case.

DR. FUSSELL: I wish to state that we have abundantly confirmed the observations of Pepper and Stengel as to the value of auscultatory percussion in the diagnosis of dilatation of the stomach. We have used it in a large number of cases in the out-patient department. An interesting proof of its value is the fact that students who are not especially skilled in the work will almost always strike the same line for the various outlines of the stomach.

DR. MELTZER: Dr. Pepper mentioned incidentally that the sounds which usually accompany the entrance of food into the stomach are of no value in the diagnosis of dilatation of the stomach. Allow me to state that when I described these sounds about twelve or thirteen years ago, I stated that usually in a normal stomach they could be heard mainly to the left side of the xyphoid, but when the stomach was dilated the larger the stomach the larger the area over which these sounds could be heard. I do not know whether this mode had been followed by Dr. Pepper when he mentioned that the sounds have been of no value in relation to diagnosis.

DR. GRAHAM: I will just mention a case in which the ordinary means of diagnosis, such as described by Dr. Pepper, were not sufficient to enable the physician to form an opinion as to dilatation of the stomach. The case was one of chronic gastritis with ordinary symptoms. We made an examination by percussion and by the other means just given, and came to the conclusion that the patient had dilatation of the stomach. On post-mortem examination we found the patient had suffered from a tuberculous peritonitis, and that the transverse colon was dilated and attached to the lower margin of the ribs and prevented the stomach from coming in contact with the walls of the abdomen at all. Although the stomach was somewhat dilated it could not be palpated during life. In such a case the only adequate method of examination I know of would be by Leube's stiff tube.

[1] The diagnosis in this case has since been verified by autopsy.

I would like to mention that I have examined for dilatation of the stomach a large number of cases of rosacea and acne rosacea, and have found it present in a considerable proportion of cases.

DR. JACOBI: In the diagnosis between carcinoma and pernicious anæmia there is one more point I believe to be very important. I have now three cases in which I have made the diagnosis between pernicious anæmia and carcinoma, which certainly is sometimes difficult. In all the cases in which I had reason to be doubtful, I found that in carcinoma the blood-cells were of absolutely normal shape, while in pernicious anæmia I expect to find poikilocytes, microcytes, and macrocytes.

NOTES ON X-RAYS IN MEDICINE.[1]

By FRANCIS H. WILLIAMS, M.D.,
OF BOSTON.

During the past two or three months I have been much interested in studying the x-rays, and with the assistance of Mr. C. L. Norton and Mr. R. R. Lawrence, of the Massachusetts Institute of Technology, who have been investigating the x-ray problem in the Rogers Laboratory of Physics, have tested the application of x-rays to medicine in various ways. Their application to surgery was soon evident; pictures of all the bones can be taken that show their structure and details with marvellous clearness; not only is the bony structure of the extremities but also that of the larger bones and of the joints, for example, the comparatively superficial joints, such as the shoulder, the elbow, and especially the ankle (Fig. 1) beautifully shown, and Fig. 2 demonstrates that the deep hip-joint and the neck of the femur are to be within our reach for the diagnosis of dislocations and fractures; the trochanters of the femur and its spherical head, and the portion of the head outside and inside the acetabulum can be photographed, as well as the whole bony structure of the pelvis, even the details of the sacrum showing. The medullary canal of the long bones, as, for instance, the shaft of the femur, is distinctly shown, and it is not improbable that we may be able to distinguish changes in the bone-marrow. Fractures and dislocations, and also diseased conditions of the bones involving change of structure or density, changes in the joints themselves, aside from the bones, may be studied with profit by the x-rays. In some of the negatives the outlines of muscles and tendons are indicated. The development of the skeleton at different ages may also be well studied.

[1] I have included in this paper some observations made soon after the meeting.

Pieces of metal impervious to the rays, such as bullets, may be located with precision. To do this two views are necessary: one to show the position from right to left, and the other the distance from the front or back.

The following cases will illustrate this use of the rays:

A patient from the Boston City Hospital, who was thought to have a bullet in his right forearm, was brought to me for examination. The bullet was readily detected by the fluoroscope about the middle of the radius, some distance from its point of entrance, which was near the wrist. I marked the position of the bullet on the skin from two points of view in order to indicate to the surgeon the size and place of the bullet. It was found in the radius, and the size corresponded to what we saw in the fluoroscope.

A patient of Dr. Charles McCarthy, of Franklin, Mass., was referred to me by Dr. George H. Monks, of Boston. She had been shot in the back ten weeks previously, the 38-calibre bullet entering through the lower portion of the scapula; but it had not been found. A photograph taken of the left side of the thorax, including the spinal column, the shoulder-joint, and the humerus, did not reveal the bullet, but showed where it had pierced the scapula and broken a rib, and at one of these points a small piece of lead seemed to have been left as it passed. I could state with confidence that the bullet itself was not in that part of the body, as with the fluoroscope we could see distinctly a piece of lead-wire only one-eighth of an inch in diameter when held on the opposite side of the patient from the observer. On the following day photographs (Figs. 3 and 4) which included the neck and upper portions of both sides of the thorax, was taken, and the bullet exactly located at the base of the neck.

My brother, Dr. Charles H. Williams, lately brought a patient to me for examination who was thought to have a piece of copper in one of his eyes. I was not very sanguine about the result of the examination, and we therefore first tested the matter in a rough way by placing a piece of bent copper-wire of about the diameter of the lead of a lead-pencil, on one of Mr. Norton's temples. The Crookes tube was placed near his temple and the photographic plate on the other side of the head, in order to make the test as severe as possible. Finding that the wire could be easily seen in the negative, even though placed far from the plate, we then proceeded to photograph the patient's eye,

which we placed near the plate to give it every possible advantage. The position of the eyeball could be distinctly seen in the picture, and in about the centre of the eye was a spot corresponding, as we thought, to the piece of copper said to have penetrated it. Dr. Williams then operated and found and removed a flat piece of copper $\frac{1}{8}$ by $\frac{1}{4}$ of an inch, which was similar in shape to what we had seen in the negative.

But I wish especially to direct your attention to some of the medical rather than the surgical uses of these magical rays, and especially to their use with the fluoroscope; in the fluoroscope with a screen of tungstate of calcium the parts of the body which are most easily passed by the x-rays appear lightest on the screen, those which are densest being darker. The lungs are easily penetrated, the ribs, clavicles, and vertebræ being in marked contrast to other portions of the thorax (Fig. 5). The density of the lungs is much less than that of the other organs and the fact that their density is increased in many diseased conditions will make the x-rays serviceable in diagnosis. Against the lower part of the right lung the outline of the upper portion of the liver is distinctly seen, and the rise and fall with the respirations easily followed. Between extreme inspiration and expiration the liver moves vertically about three inches. Below the left lung is seen the spleen, and by raising and lowering the Crookes tube while looking through the fluoroscope one may so adjust the tube as to follow the outline of the spleen completely, and also to see the lower border of the liver on the right side. By looking through the body from side to side with the fluoroscope, the observer being on the patient's right, the whole outline of the great mass of the liver may, under favorable conditions, be seen hanging in the vault of the diaphragm. On examining one patient, I found that he could move his liver by inspiration and expiration less than an inch, and as there was a history of localized peritonitis a year previously, it is possible there were adhesions limiting the movement of the liver.

The pulsations of the heart may be followed with the fluoroscope, not only the ventricular, but also the auricular contractions and dilatations.

In the following cases the usual physical examination and that made with the fluoroscope corresponded very well:

CASE I.—The first medical case I examined was that of a man with an enlarged heart (seven inches in transverse diameter). I found that the outline of the heart, as seen from the front of the body through the fluoroscope, corresponded in a general way to the outline drawn on the skin with percussion as a guide. It was interesting to note that the heart could be made out through the man's waistcoat and two shirts.

CASE II.—In one of my patients, who was recovering from pneumonia, the signs by auscultation and percussion, which were only in the lower part of the right chest, were moderate dulness, slight bronchial respiration, and a few râles two fingers' breadth above the right base in the back; nothing in the chest in front.

By the fluoroscope: Clear area at right apex; darker area in lower right chest, apparently extending about two inches above level of liver.

CASE III. was a patient of one of my colleagues, who was suffering from tuberculosis of the right lung. His hospital record was as follows:

January 31, 1896. C. B., aged twenty years. Left lung negative; dulness at right apex, and just below this an area of tympany, over which is heard amphoric breathing. At apex expiration prolonged, and fine moist and crackling râles. Dulness in back nearly to scapula, with numerous fine, moist, and crackling râles.

April 14*th*. Dulness in upper two-thirds of right back; tubular respiration on top and rather obscure breathing below, with rather dry râles over area of dulness. Percussion at second space dull rather than tympanitic. Tubular respiration rather more circumscribed, and most marked toward anterior axillary line. Fine, dry râles, increased by cough, extending about two-thirds down.

After looking at this patient from behind for a moment only, the difference in the amount of rays which passed through the two sides of the chest was very striking, as seen through the fluoroscope, the diseased lung, as I had predicted, being darker throughout than the normal lung. The ribs on the left side were much more distinct than those on the right.

CASE IV.—A. B. In this patient symptoms of tuberculosis began six weeks before she came under my care. I found the physical signs as follows:

On the right side, in front, increased voice-sounds and increased vocal fremitus from apex to third rib, with high-pitched medium moist râles above and just below the clavicle, not lower than the second rib. *Behind:* Dulness, moderate bronchial breathing, and moderate number of râles from apex to one inch above angle of scapula. By fluoroscope: Examination of lungs showed a darker area in right upper half of chest, the rays passing through the left apex very well.

As we have seen by the cases just cited, the fluoroscope is already of service in assisting the physician to determine the position and extent of some of the diseases of the respiratory system and the position and size of the heart, likewise the position, size, and mobility of

the liver and spleen. By its aid we may in some cases of tuberculosis have an earlier warning of the disease than by the other physical signs hitherto at our disposal. To make these observations it is necessary to have good apparatus and to be able to vary readily the position of the Crookes tube while looking through the fluoroscope. We used a Wimshurst machine with twelve plates, each twenty-six inches in diameter, designed by Messrs. Norton and Lawrence, and it has given excellent results, much better than those obtained with the alternating current; the pictures with the Wimshurst machine being sharply defined and clear and the tubes not being destroyed. A photograph of the bones of the hand can be taken by this machine after an exposure of five seconds or less, although a longer exposure gives more detail.

In using the fluoroscope it is important to bear in mind the relative position of this instrument, the Crookes tube, and the organ which is under observation. For example, in examining the heart a good position for the tube is about on a level with the heart in front of the patient and a little to the right of his median line; the patient should not face the tube squarely, but should be placed with his right side turned a little toward it; the observer, standing behind the patient and holding the fluoroscope to the left back of the latter, thus sees the shadow of the apex of the heart projected on the screen of the fluoroscope far to the left, even touching the left posterior axillary line, thus bringing a large part of the heart into view.

It is sometimes of service to be able to vary the length of the spark while observing with the fluoroscope, as the character of the picture changes with the character of the light. For instance, with a long spark the medullary canal of the long bones is distinctly visible, while with a short one this disappears and the bones become darker.

Some months ago Mr. S. C. Keith, Jr., of the Biological Department of the Massachusetts Institute of Technology, brought cultures of bacteria to Mr. Norton, for exposure to the x-rays. Tubes of melted nutrient gelatin were inoculated by Mr. Keith with the bacteria named below, and this gelatin was then poured out into a sterilized Petri dish, over which it formed a thin layer, and allowed to cool. One-half of the dish was covered with a thick plate of brass, through which the x-rays do not pass, and the dish was then put into

a tight pasteboard box which was placed about four inches from the Crookes tube. The bacilli used were exposed as follows:

Bacillus anthracis	5 minutes.
Bacillus typhi abdom.	5 "
Bacillus " "	20 "

In the above-mentioned experiments the Petri dishes had glass covers; in the following, very thin aluminum covers were used:

Bacillus coli communis	1 hour.
Bacillus prodigiosus	1 "
Bacillus "	2 "
Bacillus "	4 "

After this exposure the Petri dishes still enclosed in the box were incubated from twenty-four to forty-eight hours at 37° Cent. Examination thereafter showed that the colonies of bacteria developed equally well on the exposed and unexposed side of the dishes.

In order to make a comparison between the effect of the x-rays and the sun's rays on bacteria, the bacillus coli communis and the bacillus prodigiosus were exposed to not very bright sunlight (the day was hazy) for fifteen minutes, the experiments being conducted in the same manner as those above described. The incubator showed that the bacteria exposed to the sun's rays were killed.

Explanation of Plates.

Fig. 1.—Foot with shoe on.

Fig. 2.—The hip-joint of a woman. The sacro-iliac synchondrosis is also shown as well as a portion of the sacrum.

Fig. 3.—The thorax of a woman.

Fig. 4.—This picture was taken with the Crookes tube on the right side of the neck and the photographic plate on the left side. The bullet was just behind the sterno-cleido-mastoid muscle. It is seen in the illustration in front of the vertebræ; the lighter area behind it is the trachea, and above this are the larynx and epiglottis, and crossing the epiglottis is the hyoid bone. The dark area at the top of the picture is the angle of the lower jaw.

Fig. 5.—Picture of the same taken from behind.

FIG. 1.

FIG. 2.

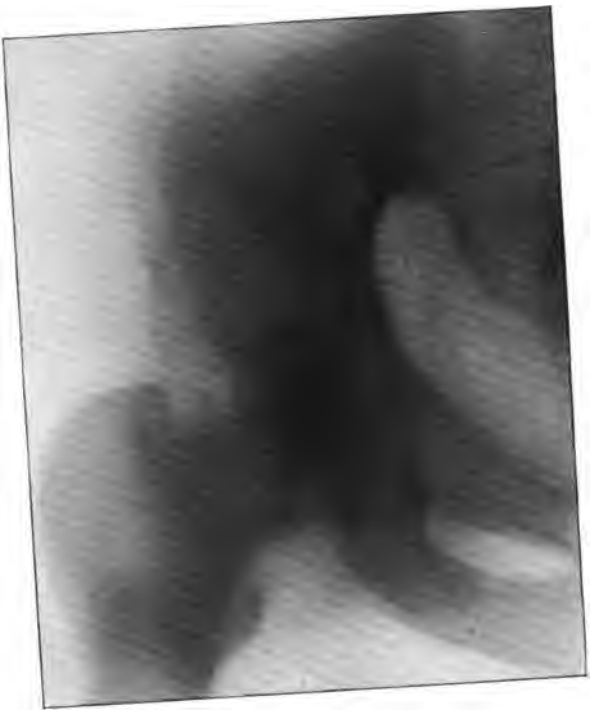


FIG. 3.

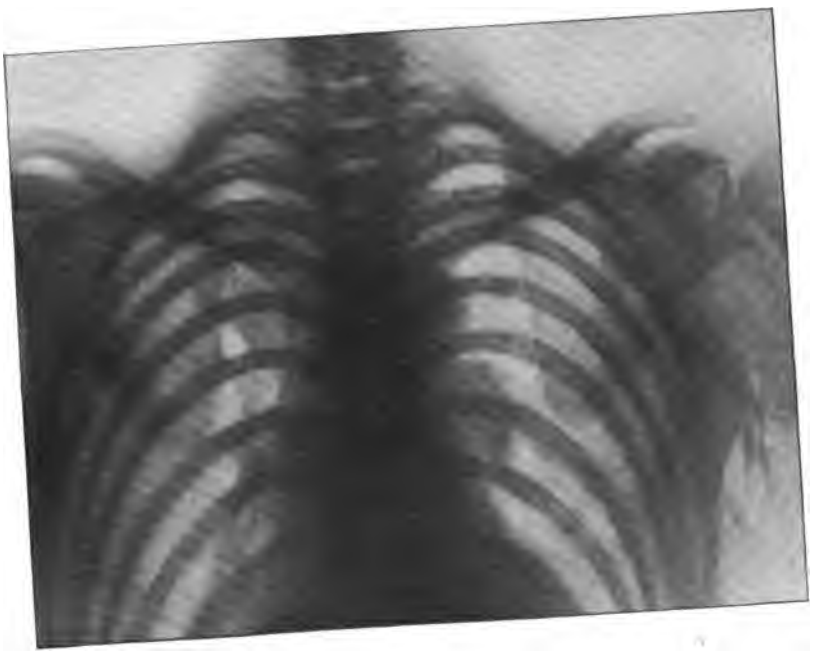


FIG. 4.

FIG. 5.

DISCUSSION.

Dr. STERNBERG: I had intended to ask permission to make a separate communication on this subject, but what I have to say will come in very appropriately in the discussion of this paper. It is very clear that the X-rays are going to be very useful in diagnosis, but some physicians have gone much further than that and have imagined that they will also be useful in therapeutics by killing pathogenic bacteria *in situ;* and various newspaper reports have been published in support of this view. The favorable results reported are not by persons known to us and are not worthy of any great attention. I received this morning from a medical officer who was at the Army Medical School last winter, and who is now at Fort Leavenworth, a letter giving an account of some recent experiments in this line. It is as follows:

FORT LEAVENWORTH, KANSAS, April 27, 1896.

TO SURGEON-GENERAL GEORGE M. STERNBERG,

DEAR SIR: I noticed an article, in a recent issue of the *Evening Star*, which quoted you as not having accepted as final the experiments of the Chicago physicians, as to the germicidal effects of the so-called X-rays when brought to bear upon certain pathogenic organisms. Pardon me if my interest in this question leads me to write the result of a similar experiment at Leavenworth.

On April 25th, Professor Blake, of the Kansas State University, delivered a lecture on the Roentgen rays and invited me to be present. I took with me, from our bacteriological laboratory at the post, pure cultures of the cholera, typhoid, diphtheria, anthrax, and pus (staphylococcus aureus) organisms, and these were exposed to the new light which he produced with the Crookes's tubes, Tesla's coils, and the use of the street current. After ten minutes' exposure the tubes were returned to the laboratory, and transplantations to sterile agar slants were made. At the expiration of forty-eight hours I examined the tubes and found abundant growth in every case. The light was genuine, because many splendid photographs of bony deformities were made and exhibited. If the ten minutes' exposure was sufficiently long, this may go to disprove the announcement of the Chicago experimenters.

Very sincerely and respectfully,

J. HAMILTON STONE,
Asst. Surg., U. S. A.

I would simply remark, further, that it can hardly be expected that any physical or chemical agency which will destroy these low vegetable organisms would not also be destructive of the living cells of animal tissue.

DR. F. H. WILLIAMS: I cut out of my paper a few lines about the action of the X-rays on bacteria in order not to take up too much time. Mr. Keith, of the Biological Department of the Institute of Technology, subjected some specimens of various kinds of bacteria, typhoid bacilli, and some others, to the X-rays for half an hour, and in some experiments for hours, and compared their growth with other bacteria from a similar source. Those which had been under the X-rays grew just as well as those which had not been so exposed.

DR. ERNST: In a newspaper account of some experiments I saw it stated that where a Crookes's tube had been held to the head of a gentleman, in an attempt to photograph his brain, the gentleman lost his hair at that particular spot. I would like to ask Dr. Williams if there is any truth in this.

DR. WILLIAMS: I have had my head in the rays for some time and I do not think I have any less hair than I had a few weeks ago.

DR. OSLER: I should like to know whether the fluoroscope can detect gall-stones. I would like to know if Dr. Williams has tried it. Apparently they are not capable of being skiagraphed.

DR. WILLIAMS: I cannot answer that question. I am waiting for a case of gall-stones to try it upon.

ON A METHOD OF RELIEVING TIC DOULOUREUX.

By CHARLES L. DANA, M.D.,
OF NEW YORK.

Tic douloureux is a form of neuralgia of the trigeminal nerve, which is so striking in its symptoms and so distinctive in its origin and course that it fully deserves its accepted position as a separate clinical type. It begins during or near the degenerative period of life, its pains are sharp and agonizing, and drive through the face like a red-hot blade; they come on intermittently in crises of intolerable distress, with sweating, lachrymation, nasal discharge, and flushing and puffing of the face.

Its course is chronic, with sometimes intermissions of a few weeks or months. The disease has been incorrectly said to be incurable. Spontaneous cure not very rarely occurs, and the natural duration of the malady in its milder forms is from six to twelve years. In many cases it shows no signs of abatement, but lasts till the patient is worn out by the agony, or terminates existence by almost justifiable suicide.

The treatment heretofore advised has been of the most various kinds, and includes nearly every narcotic in the Pharmacopœia, besides tonics, counter-irritants, electricity, hydrotherapy, and surgical intervention. In the *Index Catalogue* I find a list of over thirty remedies, which are recommended as having proved efficacious. Single cases of cures have been reported from the use of iron, aconitia, glonoin, salicylates, iodides, gelsemium, and other drugs, but I find no record of any series of cases treated medicinally with success. Of late years the surgeon has been most in evidence in the treatment of tic, and, if one could believe in his therapeutical reserve as much as one does in his operative zeal, the therapeutics of trigeminal neuralgia might be considered in a very satisfactory condition. My personal experience, however, leads me to think that surgical interference

usually gives only temporary relief. While I have not attempted to get statistics on this point, for this is outside the purpose of my paper, I have, during the last year, met three patients who had been operated upon, and whose neuralgia came back in a few months. One of these was a case in which the patient had had the Gasserian ganglion removed by Hartley through a lateral opening in the skull. This patient had not only relapsed but had become insane.

In the present state of therapeutics of tic douloureux, therefore, I think that no excuse is needed for presenting the description of a method of treatment which I have now been pursuing for two years at my clinic at the Post-graduate and in my private practice. While I do not offer it as a specific, it has certainly accomplished much more than any previous plan.

The method consists in the following procedures:

1. The hypodermic injection of massive doses of strychnine.

2. The administration of stimulants, such as iodide of potassium, and of tonics, including especially large doses of tincture of iron.

3. Rest in bed, with light diet and diuretics.

Let me say here that I owe to my friend, Dr. George R. Elliott, Instructor in my Clinic, the suggestion of using the massive doses of strychnine, and I am indebted to him for assistance in treatment and in securing notes for this paper.

The treatment admits of no half-way measures. The patient must take the full course, and sometimes even a second or third course.

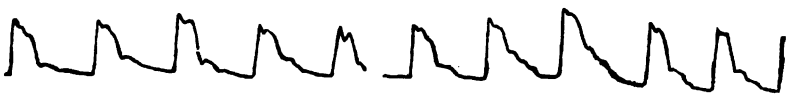
1. *The Use of Strychnine.* This is given in single daily doses, hypodermically. I usually begin with gr. $\frac{1}{30}$, and this is very slowly increased until by the fifteenth or twentieth day gr. $\frac{1}{6}$ to $\frac{1}{4}$ is given. Most patients cannot take over gr. $\frac{1}{5}$, an excess being shown by stiffness in the jaws and legs, trembling, and nervousness. Sometimes the largest doses are not well borne, and are not advisable, but this is rare. I have noticed, as has Dr. Elliott, that the large doses, gr. $\frac{1}{15}$ to $\frac{1}{5}$, often have a decidedly anodyne effect, quieting the patient for hours, like a dose of morphine. Sometimes the largest doses temporarily increase the pain, but this is certainly rare. The best results are in these who feel this anodyne effect.

The peculiar effect of strychnine in massive doses is well shown in a patient now under treatment. An injection of gr. $\frac{1}{6}$ produces at first a slight spasm of pain directly after the administration; this lasts five

or ten minutes, then gradually subsides; meanwhile the patient grows quieter, and enters into a half-somnolent state, as though she had received morphine. Meanwhile the pulse is slightly slowed and strengthened, the amplitude of the pulse-wave is lessened, the arterial tension increased, the vessel is better filled, and the heart-beat is stronger.

This is shown in some tracings taken from the patient E. B., Case IV., which I present here:

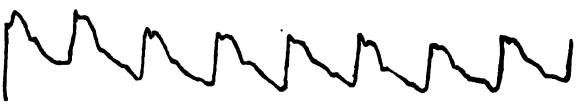
CHARTS SHOWING EFFECT OF LARGE DOSE OF STRYCHNINE ON PULSE-RATE AND TENSION.



I. Before injection of strychnine. Pulse-rate, 84, slight pain.

II. One-quarter hour after injecting gr. $\frac{1}{6}$ strychnine; more pain.

III. One-third hour after injection; slight pain.



IV. One-half hour after injection; pulse-rate 78. Patient drowsy and lying as if somewhat stupefied; pain nearly gone.

Occasionally, as we know, tic douloureux is associated with a motor tic, involving the seventh nerve, and even the tongue and masseters (twelfth and fifth). This motor spasm does not contraindicate the use of strychnine. One patient came to me unable to open her jaws on account of masseteric spasm, and for a time she had to be fed with a spoon. Under the use of strychnine the spasm entirely ceased, and in two weeks she could chew her food (Case IV.).

After receiving the maximum dose it should be continued for a week

or ten days and then gradually reduced, so that by the end of five to six weeks the beginning dose is reached. The drug is then stopped, and is replaced by others.

2. *The Use of Iodides and Tonics.* The patient is now placed on potassium iodide, gr. v *ter in die*, increased to gr. xx; and tincture of iron, ♏ v, increased, if possible, ♏ xxx, and well diluted. In some cases salicylate of potassium replaces the iodide, or nitroglycerin is added to the iodide or iron.

I find in at least one-fourth of my cases that there is a trace of albumin in the urine, with evidences of interstitial nephritis and arterial sclerosis. It is this fact that obliges one to use a certain amount of discrimination in the terminal management of the disorder. The importance of arterial sclerosis in the pathology of tic I have already shown, but I do not propose to enter upon this branch of the subject here.

3. *Rest in Bed.* This is a feature in the management of tic whose importance has, I have no doubt, been recognized by others, but I believe it cannot be too stringently insisted upon. It should secure for the patient at the same time freedom from anxiety, physical rest, an equable temperature to the exposed nerve, and capacity to take up more strychnine without unpleasant symptoms. It is usually sufficient to allow the patient to rest at his home, but this can only be allowed if he is free there from any disturbing domestic or business anxieties. In some cases it is sufficient to allow the patient to rise at noon and remain the rest of the day on a lounge, but this concession I yield rarely and with reluctance. The room must be kept as nearly as possible at 68° F., and the air should be moderately humid. At the end of four weeks I allow an outing of two hours daily, and at the end of six weeks he can resume his ordinary avocation. In obstinate cases the patient after the treatment, though feeling vastly better, still has some twinges of pain. He must then be promptly put through the course as before. Sometimes, also, the pain returns in a few weeks, and then a second treatment is needed. Twice I have found this additional treatment indicated; in both cases it was successful.

The foregoing description shows that my plan of treatment is not the simple and easy application of a specific. It involves a good deal of personal sacrifice by the patient and careful watching by the physician; but I rarely find patients who are unwilling to undertake it, and

it certainly has less terrors than the modern surgical operation, which endangers life and reason without securing positive cure.

REPORT OF CASES.

CASE I.—Louis V., aged forty-three years, German. The family and previous history are negative. The patient's trouble began ten years ago, with a slight pain involving the right upper lip, and, later, the eye and brow. The attacks of pain increased gradually in severity. They would leave him occasionally for periods of about a month, then would return for two or three months. Although his teeth were apparently perfectly sound, he had had a number of them extracted without any relief. The patient's general health continued fairly good, although, during the paroxysms, his bowels would get constipated. He ascribed the cause of his attack to exposure to heat, cold, and wet during the construction of an ice house. He had, during the past ten years, consulted over ten different physicians, and had taken enormous amounts of medicine of various kinds, but he had never had any permanent relief.

He came to my clinic on May 1, 1894, and was at once placed upon hypodermic injections of strychnine, which were given by Dr. George R. Elliott. Dr. Elliott increased the injections gradually, until he was taking a quarter of a grain of strychnine daily. The paroxysms ceased, and the patient was discharged, cured. He has had no return of the trouble.

CASE II.—I. F., aged seventy years, married, business. This patient was referred to me by Dr. J. Howard Morgan, of Westerly, R. I. Hereditary history negative; had always been a healthy man, regular in his habits, and temperate in every way. No history of syphilis, gout, or rheumatism. During the last few years of his life he had not lived as comfortably, nor had his nutrition been looked after as carefully as formerly. There was no history of mental shock or worry.

When I first saw him, his disease had lasted, with intermissions, for four years. March, 1891, it began with pain in the supra- and infra-orbital nerves on the right side. An upper incisor tooth was removed, and the pain was relieved for a few weeks. It returned again, and under the use of arsenic and iodide it disappeared. Three months later it again returned. This time a canine tooth was extracted, and after this he had no severe pain until April, 1893. Under the use of arsenic, gelsemium, the galvanic current, and later, strychnine, the attack gradually lessened. But it returned again in November, 1893, and from November until March, 1894, a period of five months, it persisted, with very slight intermissions. During this time he was treated by Dr. Morgan with strychnine, quinine, phosphoric acid, iron, arsenic, cod-liver oil, extra food, galvanism, and he was systematically given acetanilide, opium, hypodermics of morphine or hyoscine, local applications of cocaine, carbolic acid, chloral, camphor, aconite, aconitia, and extract of cannabis indica; blistering was also employed. In spite of all this, he got

no relief, and came under my care in the latter part of March, 1895. I placed him upon an extra diet, obliged him to keep very quiet, though I did not confine him to bed all the time, and gave him daily hypodermic injections of strychnine, increased to gr. $\frac{1}{3}$. In about four weeks his pain was relieved and he returned home. Five weeks later he had a slight return of his trouble, and was again placed under similar treatment. This time, however, the injections were given daily for only nine days, and then about twice a week for a couple of weeks. He was soon relieved, and has had no return since, a period of nearly a year.

In this case I found evidences of arterial sclerosis and interstitial nephritis, there being a slight amount of albumin in the urine, which later disappeared.

CASE III.—Mr. James McK., aged sixty-three years, married, business. This patient was referred to me by Dr. Meynen, of Jamaica, L. I., and it was by Dr. Meynen that the treatment was carried out. The patient is a man of good physique and of temperate habits. No history of gout, alcoholism, or syphilis. When he was about thirty-two years of age he suffered from intense headaches, involving the left temporal region, and lasting four or five hours. The pain felt like a red-hot iron in the brow. He saw flashes of light with it, but had no nausea. This trouble disappeared in about five years. He has had occasional slight attacks of rheumatism, always in the left hip.

The present trouble began two years ago, with an attack of grip. He was then laid up in bed for twelve days, but in the following summer, that is, in the summer of 1893, he had what he considered malaria, and suffered from depression and physical weakness, drowsiness, but had no chills. From this time his teeth began to trouble him, especially on the right side, in the upper jaw. With this there were occasional neuralgic pains in the upper jaw. He had the teeth removed, and got better for a month; the pain then returned, and has been with him continuously ever since, that is, for about a year and a half. The pain came on in agonizing twinges, the attacks lasting sometimes an hour, and associated with congestion of the eye and face. There was no lacrymation or nasal flow. The right pupil was larger than the left. The face was somewhat congested on the right side.

When examined by me, November, 1895, he looked like an originally robust man, but was weak and somewhat anæmic. His pulse was rapid, irregular, and weak. He had not lost much weight from his illness. There were no objective signs as regards the heart, lungs, stomach, or abdominal viscera; no anæsthesias or spasms of the face. The urine had a specific gravity of 1010, and showed a trace of albumin. He was placed under treatment at home, and hypodermic injections were given according to the method outlined. He improved, and at the end of six weeks was considerably better, but not entirely relieved. Dr. Meynen, at my suggestion, then again placed him under the same course of treatment, and at the end of about four weeks the pain had entirely disappeared, and he has been free from it ever since, now four months.

CASE IV. Eliza B., aged fifty-eight years, married. There is a history of rheumatism in the paternal branch of the family. Patient had three living children; she has lost three, and had three miscarriages. No alcoholism or syphilis. Had suffered from occasional attacks of bronchitis. Eighteen years ago was treated for sciatica. Present disease began six years ago. At that time she had an attack of grip, from which she did not promptly recover. During the convalescence she was bitten on the lip by a bird. Shortly after this she began to suffer from neuralgia on the left side of the face. The pain involved the lower jaw, and, to some extent, the upper and the left side of the tongue. Some time before this neuralgia began she had had a moderate degree of motor tic on the right side of the face.

When seen by me she was a weak, anæmic-looking woman, presenting an aspect of great suffering. The right side of the face twitched; the left side, which was the seat of suffering, was frequently congested during the attacks of pain. Those would come on nearly every hour, lasting for fifteen or twenty minutes. She had often with them headaches over the right eyebrow, and occasionally she suffered from short attacks of unconsciousness and fainting. There was no digestive trouble or cardiac disease; there was no albuminuria, but the arteries showed decided sclerosis, and the urine was 1012. She was placed upon treatment and the pains were relieved, she having no return of them until sixteen months later. Then they came back in much the same way as at first. She suffered from neuralgic attacks in the left jaw and lower part of the face, to some extent in the upper jaw, and with burning pain and paræsthesia in the left side of the tongue. Along with this there was much spasm of the muscles of the jaw, so that she could not open the mouth; there was salivation, and at times lacrymation and nasal flow. The mobile spasm of the right side of the face was also still present. She was sent to Bellevue Hospital, and placed under treatment there. Under injections of strychnine the masseter spasm was speedily relieved; in three weeks the facial spasm was also nearly gone, and she was almost free from pain. At the end of four weeks she was greatly relieved, but not cured. She had at this time no albuminuria; the urine was about 1018; average daily amount, thirty ounces. She continued under treatment until June 1st, by which time (two months) she was practically free from pain, and entirely free from spasms.

CASE V.—Thomas S., aged fifty-four years, married, telegraph operator. Came to my clinic first in January, 1896. Family history is negative. Present history: He had never had specific trouble, had been a man of temperate habits. In the last few years he had been subjected to a great deal of worry. Three and a half years ago he first began to suffer from the neuralgia. The pain appeared first in the right side of the tongue; it soon after extended and involved the whole jaw. The pain came in paroxysms, affecting the tongue, lower jaw, and occasionally the upper jaw. They could often be stopped for a time by pressure on the chin. His appearance was that of a very weak, anæmic man, the physiognomy being that of a case of Bright's

disease; an examination of the urine showed a decided trace of albumin, with low specific gravity. The right pupil was dilated, the right palpebral fissure larger than the left; there was tremor in both hands, and no mobile spasm of the face or tongue; no anæsthesia or taste disturbance. The teeth were all good, but he had had all the molars of the right lower jaw extracted, without giving him any relief. There was some deafness in the right ear, owing to an old-standing catarrh. Vision was good. The heart showed hypertrophy and a systolic murmur at the apex, and the arterial tension was high. He had albuminuria. The patient, during his boyhood, had had a resection of the left knee, due to a tubercular swelling.

He was sent home and the treatment carried out by his family physician, but it produced no results whatever. The very large doses of strychnine seemed to increase the pain. On questioning him, however, regarding the method of treatment, I found that it had not been carried out in all the details, as I had wished, owing to some misunderstanding. He got the rest and he got proper food, but he did not get the continuous effects of the large doses of strychnine. The fact that he was decidedly anæmic, that he had a marked interstitial nephritis, and a very decided cardiac disorder, was also much against him. So I do not think that the case can be fairly charged up as showing the uselessness of the treatment in ordinary cases.

CASE VI.—This patient, a man, aged sixty years, was under the charge of Dr. George R. Elliott. He had suffered for ten years from tic douloureux in a severe and typical form. He had obtained no relief, except for a short period of time. He was placed under large doses of strychnine, with rest. His pains were entirely stopped for six months, this being a much longer period of relief than he had ever had before. His pains then returned. The treatment was applied again. The patient lives in Western New York, and no reports have been had of his present condition.

CASE VII.—Tobias H., aged forty-seven years. Had suffered from a painful neuralgia of the inferior dental nerve on the left side for nine years. Two years ago he was operated upon by Dr. Abbe, who removed a portion of the inferior dental nerve. He was relieved for about a year. The disease then returned, and he was operated upon again, with partial relief. He was then placed upon strychnine treatment, and obtained under it relief, but not complete. He is still under treatment, but has been unable to take rest from his work, hence the effectiveness of the method cannot be fairly tested.

CASE VIII.—Miss R., aged sixty-eight years, a patient of Dr. R. H. Sayre, to whom I am indebted for notes, suffered from a neuralgia of the brachial plexus, following a fall in 1893. This extended to the fifth nerve in the following spring, 1894. The inferior dental nerve was most affected, but the pain at times involved the middle branch also. She suffered continuously from this pain until the spring of 1895, and she was, therefore, a victim to neuralgic pain for over a year and a half, when she was placed upon the strychnine and rest treatment. I saw her, in consultation with Dr. Reginald H. Sayre, who carried out the treatment. Dr. Sayre writes me that the re-

sult was distinct and prompt, and she was very well during the ensuing spring and summer. In the fall, owing to a death in the family and overwork, the pain appeared again, though less severe and of a more intermittent character. She was placed on the treatment again, and has been fairly well since. The duration of her treatment was about three months, though she did not receive large doses of strychnine all this time.

An analysis of the foregoing cases shows that there were two women and six men. The ages ranged from forty-three to seventy years. The branches of the trigeminal nerve most affected were, in six, the second or the second and one other branch. The duration of the malady before treatment by me ranged from two to ten years, averaging six years. Relief was obtained in all but two cases of the eight, and in one of these the method was not fully tried. The duration of the relief in five cases has been from one and a half to two years. In two cases treatment was finished four months ago. In three cases there was a slight albuminuria. In one case the disease was complicated with a motor tic, and in one case it was complicated with severe heart lesion, as well as albuminuria. The maximum doses of strychnine in all cases reached $\frac{1}{6}$ to $\frac{1}{4}$ of a grain.

Allowing for the fact that some cases of tic are relieved by ordinary measures, and that some cases have normal periods of relief, it remains proven to my mind that the special treatment here described has a very positive effect on the course of the disease in uncomplicated cases. It produces long periods of relief, and in most instances a final cure.

After much disheartening experience with aconitia, iodide, gelsemium, salicylates, tonics of various kinds, electricity, etc., I feel sure that I have never got hold of any method of treatment that has been so helpful. I have, therefore, felt that it would not only be a satisfaction to myself, but a duty to present the method to the profession for their trial.

DISCUSSION.

DR. J. J. PUTNAM: Anything which offers a new prospect of relieving these cases should be warmly welcomed, and I think we shall all be extremely glad to try Dr. Dana's method. At the same time, it does not seem to me quite fair to use the term "cure," even in a provisional sense, because the longest time he has watched his patient is two years, and we know that, oc-

casionally, in spite of the fact that unfavorable conditions seem to persist, relief may occur spontaneously for this time and even longer.

Our experience in Boston with operations has been fairly successful, especially since the more thorough deep operations have been done. The cases relapse only after a long time, and occasionally they do not relapse at all.

My own experience with aconitia has been moderately successful. We ought to classify these cases, because probably in some of them a considerable degree of neuritis is present, whereas in others there may be a change causing neuralgia without neuritis. In the former case, where neuritis is present, it would seem as if the nerves were really a foreign body and to be gotten rid of by operation.

DR. JANEWAY: If one is using aconitia he must know what aconitia he is using. I know that Dr. Starr and myself found that the aconitia dispensed at one of the best drug stores in New York had no effect on *tic douloureux*, while Duquesnel's aconitia, gotten from elsewhere, had a marked effect. In one gentleman on a very small dose of aconitia there was relief with very little tendency to recurrence. When that tendency developed, the administration of croton chloral in ten-grain doses, reduced to five, was followed by a complete absence of tic running over a considerable space of time. I was struck by the small dose of aconitia, particularly when associated with croton chloral at night, which was beneficial. This gentleman had a previous attack of *tic douloureux* and that was relieved simply by bromide.

I had previously seen a case where another plan succeeded, namely, the administration of opium, followed by considerable doses of tincture of aconite, in which we get the aconitia and the different products of aconite. There can be no doubt that some of the aconitia in the market is absolutely valueless as regards its effect in tic.

DR. H. M. LYMAN: I want to ask Dr. Dana if this treatment was used indiscriminately without regard to classes of neuralgia?

DR. WHARTON SINKLER: Dr. Dana mentions as an accessory to his treatment with strychnine certain hygienic measures, as follows: The keeping of the patient absolutely at rest in bed, keeping the temperature of the room even, and removing from him care, anxiety, and worry. These measures are often in themselves sufficient to benefit the patient greatly, and I think if we would observe these points in the treatment of *tic douloureux* with almost any remedy we would get far better results than we generally do.

DR. BOND: I rise to supplement the remarks just made by Dr. Sinkler, as I believe these cases often have evidences of nephritis, and the patients recover from the *tic douloureux* often as much, perhaps, from the fact that they are put to bed and have light saline cathartics as from the injections of Dr. Dana.

DR. HARE: I would like to ask whether these massive doses of strychnine were kept up for as long as two weeks?

DR. DANA: Yes.

DR. HARE: Have you noticed any conditions of irritability of the nervous system as shown by mental disorder? I have had cases not of this character, but of illness in which strychnine in the dose of one-tenth of a grain three times daily by the mouth for two or three weeks caused, in one instance, delusions of persecution, and, in another instance, a tendency to suicide. In one case the attending physician was quite convinced that the strychnine was responsible, because every time he stopped the strychnine the symptoms disappeared, and *vice versa*.

DR. MELTZER: I would like to ask Dr. Dana if the effect of the injection might not have been one of suggestion. The patients who see such an injection might expect it to work like morphine. I would also like to mention that in two typical cases of *tic douloureux* I succeeded very well with a hypodermic injection of antipyrine. It was very painful at the time of injection; the relief, however, has lasted over two years.

DR. DANA: In regard to the effect of suggestion I think it is possible that that may have great influence, although I am unable to say positively about it. It has been suggested that, perhaps, simply the water stops the pain. I do not pretend to offer any explanation, but I give an injection of strychnine and that usually stops the pain. The injections are usually made in the neck or cheek, but sometimes in the arm.

As to the effect upon the mind, I have never seen any ill-effect or any peculiar effect in any way. What is rather curious is that in these cases after a person has had a maximum dose, there is a slight increase in the muscular irritability, but not much. The disappearance of a masseteric spasm under this drug is rather interesting.

In regard to the matter of rest, I will say that one or two cases got well without taking much rest, still I believe that rest is most essential.

As for the application of the treatment according to the cause of the disease, I think that the treatment is directed to the cause of the disease. I think tic has but one cause, and that is an arterio-sclerosis; that is the underlying condition, and there is exhaustion and general œdema associated with it, and the treatment meets these indications. I do not include in *tic douloureux* the neuralgias of tabes, or brain tumors, or those forms that are symptomatic.

I quite agree with Dr. Janeway as to the unreliability of aconitia. I have had the same experience that he has had. Even when you get good aconitia it will not always do any good to the patient.

It is only justice to say that most of these cases had been hammered away at with all kinds of drugs before receiving the treatment I have indicated. I quite accept a suggestion of Dr. Putnam that the word "cure" is not the proper one.

THE SIGNIFICANCE OF PATHOGENIC SPIRILLA IN AMERICAN SURFACE WATERS, WITH A DESCRIPTION OF ONE ISOLATED FROM THE SCHUYLKILL RIVER AT PHILADELPHIA.

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SINCE the discovery by Koch of the spirillum of Asiatic cholera, many more or less similar spiral bacteria have been detected in materials and in places other than those closely connected with an outbreak of cholera. This is more especially the case since the recent epidemic in Hamburg. Many of the vibrios that have been described and claimed to be similar to the cholera spirillum possess but few peculiarities that would lead to confusion on the part of one familiar with the characteristics of the genuine cholera organism. On the other hand, a considerable number of forms have been detected in water, and in the stools of individuals suffering from other maladies, that possess so many of the characteristics of the true cholera spirillum that, without a specific reaction for this organism, their absolute differentiation is often a matter of extreme difficulty, and frequently of impossibility. In consequence, opinion has been divided as to the relation between the genuine comma bacillus of cholera and the organisms that simulate it; some believing them to be but different varieties of the same species, while others hold that they are definite and distinct species that resemble one another in only certain conspicuous group characteristics. There has therefore been for some time an active controversy between the supporters of these views.

The principal obstacle to the final settlement of this discussion seems to be removed by the discovery by Pfeiffer[1] of a specific relation between the serum of animals immunized from Asiatic cholera and the organism that causes the disease. Pfeiffer has found that the serum of the blood of guinea-pigs that have been rendered immune from Asiatic cholera when injected into the peritoneal cavity of non-immunized animals affords protection to them against intraperitoneal inoculation of otherwise fatal doses of the cholera spirillum by inducing in the tissues of the animal into which it is injected a peculiar germicidal power through which the living organisms are actually disintegrated. He found further that if the animal thus treated be inoculated with vibrios that are sufficiently like the cholera spirillum to cause suspicion, but which are not genuine cholera spirilla, as may have been rendered probable or certain from other data, no such disintegration occurs, or if the animal be inoculated with a mixture of cholera spirilla and other similar spiral forms, only the cholera organisms are destroyed.

This important announcement has not thus far been refuted. On the other hand, it has met with abundant confirmation, especially through the investigations of Dunbar,[2] who has employed the test for diagnostic purposes upon a fairly large group of suspicious vibrios, and has found the results to accord with opinions previously formed from other data as to the nature of these organisms. From this standpoint, therefore, it seems that the differentiation between the several suspicious species and the genuine cholera spirillum can be made with certainty and comparative ease through the employment of the specific cholera serum.

More recently Pfeiffer and Vagedes[3] have described a microscopic reaction that occurs when the cholera spirillum is examined in a drop of serum from an animal very highly immunized from Asiatic cholera. This reaction consists in almost instantaneous cessation of motion on the part of the spirilla and their rapid conglomeration into masses. After twenty minutes in the incubator no morphological change is observed in the vibrios. After twenty-four hours the retarding influence of the serum seems to have disappeared and there is evidence of

[1] Pfeiffer: Zeitschr. f. Hyg. u. Infektionskrankh., Bd. xviii. p. 1. Ibid., Bd. xx. p. 198.
[2] Dunbar: Ibid., Bd xxi. p. 295.
[3] Pfeiffer and Vagedes: Centralbl. f. Bakteriol. u. Parasitenk., Bd. xix. p. 385.

development of the organisms. They state that the motility of only the cholera spirillum is influenced by this serum.

As has been already stated, the striking morphological, biological, and pathogenic resemblances between many of the cholera-like spirilla that have been found and the true cholera bacillus have led many to believe that they are nothing more or less than varieties or modifications of one and the same organism. The fact, as pointed out by Dunbar,[1] that the most suspicious forms have been found in waters of localities in which cholera had either existed or appeared subsequently lends a measure of support to this view; this, together with the observation that genuine cholera spirilla have occurred in these waters during the same seasons in which the other varieties were detected, serves to further confirm the belief in the very close relationship between the several varieties.

The finding of suspicious spirilla in the waters of western Europe in localities that have not been visited by cholera, though pointing to their lack of identity with the true cholera bacillus, does not positively contraindicate an identity under the conditions existing at the time of the discovery. We must bear in mind that during the past three or four years there have been numerous outbreaks of the disease at many points in that country, and one can readily conceive of the transportation of the genuine cholera spirillum from places in which cholera is epidemic to neighboring localities free from the disease by means of water-courses. While this may result in the reproduction of cholera there is also justification for the opinion that this may occur without cholera being of necessity the result of such transportation, because of the modification in disease-production properties that the organism may experience by its more or less long sojourn under the unfavorable conditions found in water.

It is plain, therefore, that while the test of Pfeiffer demonstrates a conspicuous difference between the genuine cholera bacillus and most of the important spirilla that are similar to it, still the view held by many with regard to their identity is supported by pretty strong arguments. We must also not lose sight of the fact that vibrios have been found and described as cholera-like that were undoubtedly genuine

[1] Dunbar: Arbeit. a. d. kais. Gesundheitsamte, Bd. ix. p. 379.

cholera spirilla that had undergone certain biological and pathogenic modifications.

Without entering into a review of the extensive literature on the subject (which is quoted in Dunbar's article[1]), it will suffice to say that the work of Pfeiffer in connection with the specific germicidal relation of the serum of animals immunized from cholera to the spirillum that causes this disease, and the absence of such relation to other similar spirilla, is thus far the only trustworthy contribution that has done aught to satisfactorily simplify this complicated problem.

An important disturbing element in all the European investigations has been the presence of cholera in the land, and in view of this it has occurred to me that it would be of importance to determine if suspicious spirilla are to be detected in the surface waters of countries that have not been visited, either recently or comparatively remotely, by Asiatic cholera, and which are sufficiently widely separated from localities in which the disease has been epidemic or is endemic, to reasonably exclude the possible importation of genuine cholera bacilli by water or other ways. Should investigations demonstrate the presence of suspicious forms in the waters of such places, it is certain that they can play no rôle in the production of cholera. It is also reasonably certain that they can bear no immediate relation to the organism causing cholera. Such a discovery, if made, would serve as additional evidence in favor of the want of identity between the cholera organism and at least some forms that simulate it in a sufficient number of important peculiarities to warrant their being classed as suspicious.

With this in view a series of investigations was begun in October, 1895, upon the more polluted portion of the Schuylkill River in its flow through the city of Philadelphia. As the last visitation of cholera to this city was in 1873, when during the months of June, July, and August there were eight cases reported, two of which proved fatal, and about the nature of all which there is room for doubt, the water of the river offers a favorable field for such studies, especially as it is at this part of its flow grossly polluted with sewage.

As the result of studies thus far made, two spiral forms have been isolated, one of which is unimportant, as it possesses none of the

[1] Dunbar: Ibid.

group reactions common to the suspicious varieties, while the other is in every respect—morphological, biological, and pathogenic—sufficiently suggestive of the cholera group to be classed among the suspicious varieties and to warrant description at this time. The method employed for their isolation is that now universally employed in such work—viz., the modification of the method of Schottelius as recommended and applied by Koch.[1] It consists in the addition to 90 cubic centimetres of the water to be studied of 10 cubic centimetres of peptone and salt solution of ten times the usual strength employed in ordinary nutrient media, so that peptone and salt are present in the entire mixture in the proportion of 1 per cent and 0.5 per cent respectively. The flask is then placed in the incubator at the temperature of 37° to 38° C. for from twelve to eighteen hours, when, without shaking it, gelatin plates are made from the surface of the fluid. If spiral forms are present they are usually abundant in the upper layers of the fluid, as may readily be seen by microscopic examination. In from twenty-four to forty-eight hours the gelatin plates, kept at from 18° to 20° C., are ready for examination. To one familiar with the appearance of the colonies of the cholera spirillum at this stage there is little difficulty in correctly anticipating the results of microscopic examination of colonies having a similar appearance.

By this means the organism about to be described has been isolated from the water of the Schuylkill and from the contents of a sewer emptying into it, the mouth of which is partly under water at high tide. Pressure of work has prevented my making systematic studies upon this water with regard to the persistency of the spiral forms in it, so that I cannot say at this time that they are always present, nor can I speak of seasonal variations. I hope, however, to obtain data on these points at some later time.

While it has been impossible to fully identify this organism with any of the suspicious spirals described by European observers, still it simulates several of them so closely in certain important details that I am reasonably sure it is not a new species, but rather a variety. For convenience of reference I propose to call it Vibrio Schuylkilliensis, though, I repeat, this is not to signify that it is considered as a distinct species. Its characteristics are as follows:

[1] Koch: Zeitschr. f. Hyg. u. Infektionskrankh., Bd. xiv. p. 319.

MORPHOLOGY. It occurs in fresh cultures as short, rather plump "commas," often with a very decided curve, often less curved and often almost straight, though never quite so (see Plate I, Fig. 1). Its ends are usually rounded or slightly pointed. As usually seen, it is a little shorter and a trifle plumper than the cholera spirillum, though this is a very variable feature and means but little. There is no special tendency to grow into long threads, though occasionally spiral filaments, varying in length from three to five times that of a single comma, may be encountered. The single cells frequently join end to end to form S-shaped figures.

It is especially prone to undergo degeneration, and involution forms are often encountered in cultures as young as sixty to seventy-two hours. Such evidence of degeneration is especially conspicuous in potato cultures after forty-eight hours at 37° to 38° C. (see Plate I, Fig. 2).

It is actively motile, and depends for this property upon the presence of a single flagellum at one of its extremities. It does not form spores.

STAINING. It stains with the ordinary watery solutions of the aniline dyes; less readily with methylene-blue than with either fuchsin or gentian-violet.

It is decolorized by the method of Gram.

Very frequently the staining lacks uniformity. The single cells will present unstained portions; sometimes the poles only will be colored, the centre being colorless; at times the distribution of the color is more irregular and marked than at others. Fresh gelatin cultures stain somewhat more regularly than do agar cultures of the same age. Preparations made directly from the blood and tissues of animals dead after inoculation with this organism usually show commas that stain irregularly.

COLONIES ON GELATIN. In 10 per cent. nutrient gelatin rendered neutral or very slightly alkaline to phenolphtalein the colonies after twenty-four to thirty-six hours at 18° to 20° C. are fairly uniform in appearance, their outline being apparently dependent upon the number of colonies on the plate. For instance, in the "original" plate where large numbers are closely packed together they appear, when examined under the low power of the microscope, as very coarsely granular masses with no sharp border, presenting in general an ap-

pearance suggestive of minute chestnut-burs. On the plates in which there are fewer they are round, sharply defined, less coarsely granular, and have usually fine irregular markings, as if they were creased or folded. Sometimes they present indistinct concentric markings (see Plate I, Fig. 3).

As growth progresses these markings may become more and more distinct, and finally give to the colony a decidedly lobulated or mulberry-like structure. This may continue without alteration until the lobulations are so marked that the appearance given in Plate II, Fig. 5, results. At 18° to 19° C. this stage may be reached in from two and a half to three days. Or, from the condition noted at the end of twenty-four to thirty-six hours, the colony may become a trifle more granular and assume a distinctly concentric arrangement of zones, or a single zone surrounding a more or less uniformly dense and granular central mass, such, for instance, as is depicted in Plate II, Fig. 7. This stage may be reached in from forty-eight to seventy-two hours at 18° to 20° C.

Again, there may be only an imperfect arrangement of concentric zones; the central mass may be much more dense, with its circumference only partly defined and surrounded by a less dense zone, as is shown in Plate II, Fig. 8.

Again, colonies are encountered that stand, in so far as their structure is concerned, between the distinctly lobulated colonies and the distinctly concentric colonies, partaking in a measure of both characteristics. Such a colony is shown in Plate II, Fig. 6.

At times lobulated colonies are seen, the lobulations of which are quite small, and very different in their arrangement from those shown in Fig. 5. Such a colony is seen in Plate III, Fig. 9.

Less frequently colonies will appear that are finely granulated from the beginning, and, beyond a few indistinct creases or ridges, take on no distinctive structure.

After about the third or fourth day, when liquefaction is actively in progress, the majority of the colonies lose their characteristic appearance. They are then seen as irregular, ragged, granular masses lying in the centre of pits of liquefied gelatin. These pits are usually surrounded by a tolerably definite peripheral zone that may be marked by microscopic, cilia-like processes, but which is more frequently irregularly granular at its edge, as seen in Plate III, Fig. 10.

To the naked eye the plates commonly have the appearance given by plates of the cholera spirillum—*i. e.*, when quite young those containing many colonies have a ground-glass appearance. As growth continues, these plates are rapidly liquefied, usually completely so, in from thirty-six to forty hours. The plates containing fewer colonies are uniformly marked by the third day with sharply cut, funnel-shaped depressions filled with clear liquid, at the bottom of which the dense cream-colored colony is seen. They exhibit no marked tendency to spread laterally, though sometimes one, sometimes more colonies will be observed on such a plate that spread laterally very rapidly, giving rise to a saucer-shaped area of liquefaction that strongly suggests the growth of colonies of Deneke's spirillum or that of Finkler and Prior.

Sometimes one or the other of the forms described above will predominate on a plate; equally as often both lobulated and concentric colonies will appear together. Occasionally all transitional forms may be detected, from the characteristic concentric to the distinctly lobulated or dahlia-like varieties depicted in the photographs.

Once in a while, more especially when the gelatin has lost part of its density through being exposed to higher temperatures than usual, only an imperfect effort at characteristic colony configuration will be observed. Under these circumstances I have noticed colonies having very much the appearance of those described and depicted by Ivanoff[1] for the colonies of the spirillum that bears his name—that is, they look as if they might be composed of convoluted threads.

From the description of Vibrio Metchnikovi as given by Pfeiffer,[2] together with the results of my own comparative studies of that organism, it is safe to say that in so far as the appearance of its colonies in gelatin is concerned, Vibrio Schuylkilliensis is practically identical with Vibrio Metchnikovi. As liquefaction becomes more and more advanced in the gelatin the plate gives off a most unpleasant odor, that it is impossible for me to describe. The reaction has now become excessively alkaline. A portion of this alkalinity is due to the presence of a volatile alkali which may readily be driven off by gentle heating, as may be detected by a bit of moistened litmus-paper

[1] Ivanoff: "Zeitschr. f. Hyg. u. Infektionskrankh.," Bd. xv. p. 434.
[2] Pfeiffer: Ibid., Bd. vii. p. 347.

held over the plate. There is also an increase in the fixed alkalinity, for by higher heating, even boiling, the reaction is still seen to be much more alkaline than is the case with the uninoculated gelatin. By the addition of sulphuric acid to the liquefied gelatin in the plates a very bright, cherry-red color is produced, evidently due to the presence of indol.

GELATIN STAB-CULTURES. In the form of stab-cultures in gelatin the appearance of the growth is essentially that of the cholera spirillum. It is usually a little more rapid, but at times is practically identical with it.

At the end of three and a half to four days there is the characteristic cup-shaped liquefaction, capped by the so-called air-bubble. The growth continues downward as a fine line along the track made by the needle. In seven or eight days the relative proportions of this picture remain about the same, though the figure made by the growth has become magnified. In three weeks the characteristic appearance of the growth has disappeared. The gelatin in the tube is from one-half to two-thirds liquefied, the liquid is covered by a dense pellicle, and at the bottom is a dense, cream-colored mass that is often twisted or root-like. (See Plate III., Fig. 11, a, b, c.)

GROWTH ON AGAR-AGAR. On meat-infusion agar-agar containing 2 per cent. agar and neutral or slightly alkaline to phenolphtalein, growth is very rapid at body temperature. In twenty-four hours the colonies will range from 1.5 to 2 millimetres in diameter. They are not especially characteristic in appearance at this time, being simply smooth, lustrous, and opaque. After forty-eight to sixty hours they are usually more dry, occasionally a little wrinkled, with at times something of a concentric arrangement of wrinkled zones. The character of the growth on agar-agar varies with the conditions offered by the medium. For instance, in meat-infusion agar-agar rendered neutral or slightly alkaline to phenolphtalein (35 to 37 cubic centimetres of normal KOH to the litre) the growth after twenty-four hours at 37° to 38° C. is very voluminous, appearing as an opaque, smooth, moist, glistening layer. After forty-eight hours it is drier, becomes more and more wrinkled, especially at the bottom of the tube, and often extends in the form of a dense pellicle over the water of condensation in the bottom of the tube. This pellicle is usually pushed a short distance up the sides of the tube. When one inspects this growth by

the aid of a wire loop it is frequently found to be in its entirety a zoöglœa or pellicle that can be easily and cleanly stripped from the surface of the agar practically *en masse*. It holds together tenaciously and can be broken up in fluid only with trouble, and then not completely. As the culture becomes older the growth gradually takes on a dirty, coffee color. These cultures give off a most pronounced odor of indol.

On agar-agar made from meat-extract and rendered neutral to litmus-paper the growth is much less voluminous and is not seen to adhere together in the zoöglœa-like way referred to above.

BLOOD-SERUM. The growth of the spirillum on blood-serum, made either according to the formula of Loeffler or in the ordinary way, after twenty-four hours at body temperature, appears as a line of depression that does not tend to spread laterally. This continues until there is a distinct track of liquefaction marking the course of the development. As growth continues this becomes more and more conspicuous, and finally takes on a dirty brown color. The liquid that collects at the lower part of the tube is covered with a dense pellicle.

BOUILLON. Bouillon becomes uniformly clouded in twenty-four hours at body temperature. Its reaction becomes more alkaline as growth progresses. A pellicle, at first delicate, later denser, always characterizes the growth in this medium.

POTATO. On potato of the ordinary reaction the growth after forty-eight hours at body temperature is very slight. At the point of inoculation there is a thin, glazed, more or less dirty yellow, shading to a brownish, deposit that is at times surrounded by a flat, dry, lustreless zone, but more frequently this zone is absent. On microscopic examination the organisms composing this growth are found to be commas in all stages of involution. As these cultures become very old (two weeks or more) the growth seems to have sunk slightly into the potato.

LITMUS MILK. In fresh milk containing a few drops of blue-litmus tincture a slight reddish tinge appears after twenty-four hours at body temperature. After forty-eight hours this red color is usually increased, and at times there is coincident coagulation of the milk, though this is not always the case. There is but little increase of the red color after the third day.

PEPTONE SOLUTION. In the ordinary 1 per cent. peptone solution growth is rapid and is usually accompanied by a pellicle on the surface of the fluid.

After twenty-four hours at body temperature a brilliant indol reaction may be obtained in these cultures by the addition of sulphuric acid alone. A similar, though usually less intense, reaction may often be obtained under these circumstances after as short a time as six to eight hours at 37° to 38° C.

In peptone solution containing three or four drops of blue-litmus tincture to 10 cubic centimetres of the solution there is seen, after twenty-four hours at body temperature, an almost complete decoloration of the lower layers of the fluid. This extends no further upward, as a rule, than the junction of the lower with the middle third of the solution. The upper part of the fluid retains its original blue color. When such a culture is gently shaken the entire fluid becomes blue. After a week or ten days a dense pellicle is present and the tone of the solution is somewhat greenish or greenish-blue. The color of the solution never entirely disappears, though the lower decolorized zone is sometimes greater than at others. In peptone solution containing 10 drops of rosolic-acid solution to 10 cubic centimetres of the medium there occurs, in addition to the pellicle formation, at first a slight diminution of the color; this is followed by a low degree of intensification, and at the end of ten days the solution is usually of an orange-red color.

FERMENTATION. When cultivated in the fermentation-tube in bouillon containing 2 per cent. of glucose at body temperature, growth is abundant, though no fermentation with liberation of gas occurs.

RELATION TO GASES. It is facultative in its relation to oxygen, though in an atmosphere devoid of this gas its growth is slower and less voluminous than when it has access to oxygen. This is a little less apparent with Buchner's pyrogallic-acid method than with the hydrogen method in sealed tubes.

In fluid media under an atmosphere of carbon dioxide in sealed tubes no growth is observed after seven or eight days at body temperature—probably because of the acidity of the medium due to absorption of the gas.

RELATION TO TEMPERATURE. It grows most luxuriantly at from

37° to 38° C. Growth is hardly perceptible at 10° C. It is destroyed by an exposure of five minutes to 50° C., though it withstands this temperature for from one-half to one minute.

PATHOGENESIS. The pathogenic activities of this organism are most conspicuously seen in pigeons and guinea-pigs, both of which are uniformly susceptible to infection by it. In a few instances in which rabbits and grown chickens have been inoculated they have shown themselves to be naturally immune to relatively large doses. Mice may be infected with comparatively small doses by subcutaneous injection. If the dose be large they die within a few hours, evidently as a result of the toxic rather than the infective action of the material used.

In determining the pathogenic powers of this organism at the time it was obtained from the river, it was soon manifest that positive results were to be obtained only through the employment of relatively large doses, as it was of comparatively low virulence. To meet this requirement a platinum-wire loop having a capacity of 6 milligrammes of a fresh agar-culture was made, and with this loop the suspensions used have been made throughout the entire series of experiments. For convenience of reference I have designated a suspension made by finely dividing one of such loopfuls of a culture in 1 cubic centimetre of peptone solution—a "normal suspension"—and such will be understood when a normal suspension is referred to in the following part of this article. In only a few cases were fluid cultures used.

INOCULATION OF PIGEONS. When inoculated with the Vibrio Schuylkilliensis pigeons may or may not die. The circumstances that determine the results of inoculation are dose and mode of introducing the organisms. When doses of from 0.2 to 0.3 cubic centimetre of a normal suspension (equivalent to 1.2 to 1.8 milligramme of a solid culture) are injected into the pectoral muscle of pigeons death results in from sixteen to eighteen hours almost without exception, whereas if the solid culture be rubbed into a superficial wound of this muscle (a pocket beneath the deep fascia) in such large amounts as 2 to 4 milligrammes, only a portion of the animals succumb. For example: Of eighteen pigeons into the pectoral muscle of which normal suspensions of this organism were injected in doses ranging from 0.1 to 0.5 cubic centimetre (equal to 0.6 and 3 milligrammes of solid culture

respectively), fifteen died and three recovered. Those that recovered had received 0.15, 0.25, and 0.3 cubic centimetre each (equal to 0.9, 1.5, and 1.8 milligramme of solid culture respectively). Of six pigeons into the pectoral muscle of each of which 1 cubic centimetre of a twenty-four-hour-old culture in peptone solution was injected, all died in less than seventeen hours.

Of eight pigeons inoculated by rubbing the solid culture into a superficial wound of the muscle below the deep fascia, only two died. Those which died had received 6 milligrammes each of the solid culture; of those that recovered, four had also received 6 milligrammes and two smaller doses—viz., 1.8 and 3 milligrammes respectively.

On several occasions an attempt was made to infect pigeons by introducing into the muscle a bit of the necrotic muscle removed at autopsy from pigeons dead after this form of infection, and though relatively large pieces (about $\frac{1}{2}$ cubic centimetre) were introduced, death did not follow in a single instance. If, however, an infusion be made in peptone solution from a similar bit of necrotic muscle, and this be injected into the pectoral muscle of a pigeon, death follows with a fair degree of regularity.

When death ensues from either mode of inoculation the most conspicuous lesion found at autopsy is that localized about the site of inoculation. By superficial inspection the inoculated muscle is usually seen to be swollen, the skin over it being somewhat tense. On stripping back the skin an œdematous condition of the subcutaneous tissue is usually observed; at times this is very marked and may extend well down along the sides and over the thighs. Occasionally it is absent. The œdematous fluid is commonly of a bright-red color. The diseased muscle is marked by parallel yellow striations that run in the direction of the muscle-fibres. Sometimes these yellow lines will be lying together as a single narrow or broader zone that completely traverses the thorax, having, apparently, healthy tissue on either side of it. Frequently the entire muscle will be marked by these yellow lines, and in consequence will present a more or less uniformly pale appearance. On incising the muscle it is found to be mottled throughout with yellow and red necrotic areas; this condition extends down to the sternum and involves the underlying muscles. Fluid may or may not exude from the cut surfaces. By microscopic examination of cover-slips from the necrotic area it is

found to be everywhere invaded by the comma-shaped vibrios in large numbers. The corresponding pectoral muscle on the opposite side is never found to be affected. It is normal in color and size, even though the inoculated muscle may be markedly affected close up to the ridge of the sternum.

The heart is contracted and is usually found to contain coagulated or partly coagulated blood. The ventricles always contain much less blood than do the auricles. The lungs and kidneys are normal. At times the spleen may be a trifle large, though it is never markedly affected. The liver is dark in color, sometimes mottled with diffuse lighter areas, but is otherwise normal.

The intestines show no departure from the normal as a rule; sometimes there may be one or two limited areas of injection.

By both microscopic and culture methods vibrios are found in very large numbers at and about the site of inoculation, practically everywhere in the diseased muscle. In fresh autopsies they are rarely numerous in the blood and internal organs, though they are to be found there in nearly all cases. For example: In fifteen autopsies, taken at random from my notes, the average number of colonies that developed from one loopful of blood from the heart was twenty-eight; in at least six other cases the number of colonies ran over two hundred, while in one or two instances only, the cultures from the blood were sterile. There is often such a small number in the blood that one may fail to find them by microscopic examination, though by culture methods they are, as is seen above, generally to be found.

At autopsies made some time after death—ten to fifteen hours—when the dead animal has been allowed to lie in a warm place the number of organisms in the blood is always greater, and if one places in the incubator the heart of a pigeon in which few or no vibrios are to be found microscopically, after a few hours the blood from it will be found to contain them in enormous numbers.

At fresh autopsies[1] the internal organs are also found to be relatively poor in bacteria.

The pathological lesions observed in pigeons dead after inoculation

[1] When possible, these autopsies were made immediately after death. Where this was not feasible the animals were placed in either the ice-chest or at an equally low temperature as soon as they were found dead, and were kept there until the post-mortem examination could be made.

with this organism are so conspicuously similar in most of their important details to those resulting from inoculation with virulent cultures of Vibrio Metchnikovi that it is impossible to rid one's self of the opinion that Vibrio Schuylkilliensis may perhaps be only an attenuated Vibrio Metchnikovi. To decide this point an effort was made to increase the virulence of the former organism, and though I have not as yet (up to April 23, 1896) been able to bring its virulence up to anything like the degree possessed by Vibrio Metchnikovi, it has still been increased to a point considerably beyond that given in the preceding statistics.

The method employed for increasing the virulence was that of passing the organism through a series of susceptible animals. After passing it through a series of twenty pigeons, each having been inoculated with the first generation on agar-agar from the tissues of a dead pigeon, its virulence was found to be about doubled when suspensions were employed, and about trebled when the solid culture was employed. Thus, for instance, from the twentieth pigeon of the series twelve pigeons were inoculated. Six received varying doses of a normal suspension, and six were inoculated by rubbing different amounts of the solid culture into a superficial wound of the pectoral muscle below the deep fascia. The results were as follows:

Pigeon	I	received	0.1	cubic centimetre.	Died in 27 hours.				
	II	"	"	"	"	Died in less than 11 hours.			
	III	"	0.2	"	"	"	"	20	"
	IV	"	"	"	"	"	"	20	"
	V	"	0.3	"	"	"	"	20	"
	VI	"	"	"	"	"	"	11	"

Results of inoculating pigeons with the same culture, but instead of injecting it as a suspension it was rubbed into a superficial wound of the pectoral muscle:

Pigeon	VII	received 2	milligrammes.	Had no effect.
	VIII	" 2	"	Died in less than 20 hours.
	IX	" 4	"	Died in 24 hours.
	X	" 4	"	Died in less than 20 hours.
	XI	" 6	"	Had no effect.
	XII	" 6	"	Died in less than 20 hours.

The injection of the normal suspension proved fatal, as we see, in all of the six pigeons, including those that received the dose of 0.1

cubic centimetre (equal to 0.6 milligramme of solid culture), while of those that got the solid culture, four succumbed, death having resulted in one of these from the dose of 2 milligrammes. Though the doses used throughout this experiment are relatively large, still the smallest of them is smaller than any that had hitherto proved fatal to pigeons by the methods of inoculation that were employed. It does not seem unlikely, therefore, that by the further passage of Vibrio Schuylkilliensis through susceptible animals we may at last reach a still higher degree of virulence; in short, establish its pathogenic identity with Vibrio Metchnikovi, the organism with which it possesses so many other points in common.

INOCULATION OF GUINEA-PIGS. Guinea-pigs are susceptible to the pathogenic activities of this organism by both subcutaneous and intra-peritoneal inoculation.

By Subcutaneous Inoculation. The fatal dose for guinea-pigs varies, according to the weight of the animal, from 0.3 to 0.5 cubic centimetre of a normal suspension of a twenty-four-hour-old agar-culture. After inoculation with this dose death ensues in from twelve to eighteen hours.

At autopsy the tissues about the site of inoculation are much injected, and usually moderately œdematous. Frequently the subcutaneous œdema is very widespread, sometimes it is much less marked.

The subcutaneous lymphatic glands, both inguinal and axillary, are red and enlarged.

As a rule, there is more or less reddening of the peritoneum beneath the point of inoculation, with at times general peritonitis. This may, however, be absent. When present it is characterized by the accumulation of a small amount of fluid in the peritoneal cavity and by the presence of isolated patches of fibrino-purulent material scattered over the surface of the liver, spleen, omentum, and the coils of intestine. On microscopic examination this inflammatory deposit is found to be rich in leucocytes, to contain a few endothelial cells, and to be invaded by vibrios in large number.

As a rule, the mucous membrane of the intestines is not inflamed, though once in a while they are found quite red and filled with dark, red-brown, semi-fluid contents; sometimes small areas of reddening will be detected, the rest of the gut being normal. The serous surface

is commonly injected, as are practically all the serous surfaces within the abdominal cavity.

The liver may be paler than usual; it may be more or less mottled, or, as is more frequently the case, present no macroscopic departure from normal. The gall-gladder may be normal, or it may contain pale, thin, straw-colored bile.[1]

The kidneys and adrenal bodies are usually acutely congested, especially the latter. The heart is filled with fluid blood. The lungs and spleen are, as a rule, normal. The retroperitoneal lymph-glands are red and enlarged. When peritoneal involvement is not present in these cases the great serous cavities contain no excess of fluid.

Cultures from the site of inoculation always reveal the vibrios in large number. Those from the blood and internal organs may be sterile, they may all contain vibrios in small number, or colonies may appear on some tubes while others are sterile. It is rare that colonies in large number appear on any but the tubes from the site of inoculation. When peritonitis occurs as an accompaniment of subcutaneous inoculation vibrios are present in the peritoneum in large number.

When death does not occur until from fifty to sixty hours after inoculation, as is sometimes the case when small doses have been used, the blood and internal organs are found to be sterile, though living vibrios may in some instances be recovered from the site of inoculation.

When the subcutaneous dose has not been sufficiently large to cause death, a painful tumefaction almost always occurs about the site of injection. This lasts for several days, growing gradually smaller and less tender from day to day. Finally the overlying skin sloughs away and leaves an open ulcer. This readily heals under a scab unless intercurrent infection occurs.

By Intraperitoneal Inoculation. The fatal dose for guinea-pigs

[1] Animals that survive inoculation, both subcutaneous and intra-peritoneal, for several days, and those in which death has occurred only after repeated inoculation with small doses of the living culture, or the toxin derived from old cultures, always present a conspicuous condition of the gall-bladder and its contents. The gall-bladder is distended, commonly very much so, with very pale, straw-colored, watery bile, in which float numerous yellowish flakes of amorphous material. By culture-tests the bile is found to be sterile. These animals are also markedly emaciated. A somewhat similar condition of the bile has been observed by Blachstein (Johns Hopkins Hospital Bulletin, July, 1891) in rabbits dead after chronic infection with bacillus coli communis. I have not, however, noticed the peculiar necroses of the liver that occurred in Blachstein's cases.

varies from 0.4 to 0.5 cubic centimetre of a normal suspension made from a twenty-four-hour-old agar-culture.

When a dose not much above the certainly fatal amount is employed death occurs in from eighteen to twenty-two hours. It is at times a little later or a little earlier than this. When a much larger dose is used death may occur in as short a time as four or five hours.

The condition of the animal after inoculation is characterized by a gradually increasing condition of bodily depression that is accompanied by a conspicuous fall in the rectal temperature. The fall in temperature begins usually in about an hour to an hour and a half after the inoculation and continues steadily until death, by which time it may have fallen to as low as 27° to 28° C. In one instance I saw the rectal temperature as low as 26.2° C. fifteen minutes before death. Sometimes there is a temporary rise in temperature for a short time after inoculation; this is, however, quickly followed by a gradual decline.

The general appearance of the animal is characteristic. It at first sits quietly in its cage, its hair becomes roughened, then its extremities are periodically extended, it settles on its belly on the bottom of the cage, often with its hind legs fully extended; from time to time there is convulsive jerking, and more or less constant trembling is seen for an hour or more preceding death. Respiration is accelerated, the nose and feet are cool, the abdomen is very sensitive to the touch and is moderately tense. When found dead it is usually flat upon its belly with legs stretched out behind it and its nose in the corner of the cage.

At autopsy the most conspicuous lesions are those of the peritoneum. It usually contains a few cubic centimetres of clear tenacious fluid. Over the surface of the liver, spleen, omentum, and intestines are scattered small patches of fibrino-purulent material. On microscopic examination these are seen to consist very largely of leucocytes, with an occasional endothelial cell. If the dose has been just sufficient to cause death, numerous stained granules are also present; these are seen lying both free and within the bodies of leucocytes. Typical vibrios are not detected, as a rule. If the dose has been very large, microscopic examination reveals the presence of vibrios in large number. Often both typical vibrios and irregular stained granules are to be seen together. Occasionally more or less degenerated, though still

recognizable, vibrios are found within the bodies of leucocytes. The pleural cavity may also contain a small amount of fluid in which leucocytes and stained granules are to be seen by microscopic examination.

The surface of the liver is irregularly covered with a thin deposit of fibrino-purulent material; otherwise the organ appears normal.

The serous surfaces of the intestines, as well as the serous surfaces generally within the abdominal cavity, especially the omentum, are more or less injected. Sometimes this is quite marked, while again it may be very limited in degree. The mucous membrane of the intestines is not usually inflamed.

The heart is relaxed and filled with fluid blood. The lungs are normal. Beyond a varying degree of congestion the other organs show no macroscopic changes.

By both microscopic and culture methods the peritoneum and internal organs are usually found to be sterile, or practically so, when the dose injected into the animal does not exceed the minimum lethal dose. If the dose is large, the peritoneum contains living vibrios in enormous numbers. Cultures from the blood and internal organs may reveal the presence of vibrios, though they usually occur in relatively small number in the blood; in a few cases I have found the blood to be sterile. Should death be postponed for forty-five to fifty hours, the peritoneal cavity, blood, and internal organs are sterile.

Inoculation of Mice. The studies upon mice have not been as extensive as those upon pigeons and guinea-pigs, but they have been sufficient to justify the following statements: The results of subcutaneous inoculation of mice with this organism depend upon the size of the dose employed. If very small doses be employed it is possible to cause death with all the evidences of a general infection, whereas if the dose be very large death occurs within a few hours and is manifestly the result of the toxic rather than the infective action of the material used. For example: Of two mice into the subcutaneous tissues of which (at the root of the tail) 0.05 cubic centimetre of a twenty-four-hour-old bouillon-culture was injected, one died in twenty-four hours and a half, and the other recovered with a slough of the skin over the point of inoculation. At autopsy upon the one that died no macroscopic lesions were noticed beyond a slight œdema surrounding the reddened tissues at the site of injection. Cultures from this

animal revealed the presence of vibrios at the site of inoculation in large number, and in the blood, liver, spleen, and kidneys in smaller numbers. If a much larger dose be employed, such, for instance, as 0.5 cubic centimetre of a similar culture, death occurs very rapidly, evidently the result of acute intoxication. Of two mice into the subcutaneous tissues of each of which such a dose was injected, one died in four hours and fifteen minutes, and the other in four hours and twenty-five minutes after the treatment. At autopsy on these animals little beyond a red and swollen condition of the subcutaneous lymphatic glands was observed. Cultures revealed the presence of vibrios at the site of inoculation and in the internal organs.

The course of the disease and the post-mortem conditions found in all animals leave little room for doubt that death results more from the toxic activities of the organism than from its powers of general infection, though it nevertheless possesses this latter property. Notwithstanding this I have not been able to produce death of susceptible animals by the injection of dead cultures, killed by either chloroform or heat, in doses of several fold that of the living cultures, or by moderately large doses (1 cubic centimetre) of the filtrate from twenty-four-hour to thirty-six-hour bouillon-cultures that were filtered through porcelain. Old fluid cultures—thirty-five to forty-five days of age—even when killed by chloroform, are highly toxic, and with them the characteristic lesions and death may readily be produced.

IMMUNITY. Scarcity of time at my disposal has prevented me from making a complete or systematic study of Vibrio Schuylkilliensis from this standpoint. Incidentally, however, a sufficient number of observations have been made to indicate a striking analogy between its protecting properties and those exhibited by the other suspicious spirilla embraced in this group.

Briefly stated, the results of these observations are as follows: In both pigeons and guinea-pigs immunity from relatively large doses of this organism may readily be induced either through the induction of tolerance to the poison contained in old dead cultures (destroyed by chloroform) or by the repeated employment of non-fatal doses of living cultures.

A single inoculation of either a pigeon or a guinea-pig with a non-fatal dose of living culture confers a condition of immunity that enables the animal to withstand a subsequent inoculation of from two to

three times the minimal fatal dose. This immunity lasts for at least twelve days, and often longer. The phenomenon is especially marked in pigeons. An interesting process is often observed in the course of efforts to immunize guinea-pigs by intraperitoneal inoculation. If a guinea-pig be inoculated by this method with a dose somewhat below the minimal fatal dose, and within a few days be reinoculated in the same way with a similar dose, death sometimes follows the second inoculation, though the first may have been borne with little apparent inconvenience. This accords with an occasional observation of Pfeiffer[1] on the reaction of immune guinea-pigs to intraperitoneal inoculation with Vibrio choleræ Asiaticæ. Pfeiffer explains the phenomenon—that is, the death of the protected animal—by assuming that the amount of toxin liberated through the peculiar disintegration of the vibrios, referred to above, is greater than the amount against which the animals had been protected.

This observation suggested the possibility of there being a similar disintegration of the living vibrios in the peritoneal cavity of guinea-pigs rendered immune from Vibrio Schuylkilliensis. With this in view, two guinea-pigs that were partially immune, having withstood two previous intraperitoneal inoculations, were selected. Into the peritoneum of each a little more than the fatal dose of a suspension of a fresh culture was injected. In ten minutes portions of the peritoneal exudate, obtained by means of capillary pipettes, were withdrawn and subjected to microscopic examination. A great variety of objects were seen, conspicuous among them being vibrios in all stages of involution. They were swollen, distorted, stained feebly, and were manifestly undergoing degeneration. Granules that took on the staining were also to be seen. After fifteen minutes the only objects found in the peritoneum were numerous granular masses, with an occasional body that might have been a vibrio, though it was impossible to state definitely. Numerous leucocytes were present. Occasionally stained granules were seen within the body of a leucocyte.

At fifteen minutes one of the guinea-pigs was killed. Cultures showed its peritoneal cavity to be sterile.

At thirty minutes the other was killed and its peritoneum was also found to be sterile.

[1] Zeitschr. f. Hyg. u. Infektionskrankh., Bd. xviii. p. 1, Bd xx. p. 198.

If a much larger dose was employed the phenomenon was not observed, as the animals were evidently not immunized to a sufficiently high degree to withstand excessive amounts.

This germicidal activity of the peritoneum of immune guinea-pigs is, as we now know, not peculiar to animals immune from Asiatic cholera, but may also be observed in animals immune from other forms of infection as well; for instance, in animals immune from infection and intoxication by the bacillus typhi abdominalis and by the bacillus coli communis.

It would have been interesting to have determined the relation of these animals to intraperitoneal inoculation with the cholera spirillum, but as reliable cholera cultures were not at my disposal I was obliged to omit the experiment.

The tests that have been made with the serum from both pigeons and guinea-pigs that have been rendered immune from moderately large doses of Vibrio Schuylkilliensis show that it contains a substance that is capable of protecting susceptible animals against the pathogenic effects of otherwise fatal doses. Thus, for instance, in one experiment, 1 cubic centimetre of serum from a pigeon immune from three times the fatal dose of living culture, when injected into the peritoneal cavity of each of two guinea-pigs, protected one of them against the fatal and the other against double the fatal dose of living culture injected at the same time as the serum. In another experiment of the same nature two out of three guinea-pigs were protected against double the fatal intraperitoneal dose of living culture by the simultaneous injection of 1 cubic centimetre of serum from a pigeon immune from three times the fatal dose of culture. The third animal of this series did not die until the end of the second day, showing a retardation of at least twenty-four hours in the appearance of the fatal result.

In another experiment a suspension was made by finely dividing a fresh culture on agar-agar in the serum from a pigeon immune from four times the fatal dose in such proportions that 0.5 cubic centimetre of the serum contained double the amount of culture necessary to produce fatal results. Into the pectoral muscle of each of two susceptible pigeons 0.5 cubic centimetre of this suspension was injected in less than five minutes from the time it was made. Neither pigeon showed any ill effects of the treatment.

In still another experiment it was found that when the serum from pigeons immune from at least three times the fatal dose was injected in the amount of 0.5 cubic centimetre into the pectoral muscles of susceptible pigeons, and this was followed within an hour by an injection into the muscle of the opposite side of double the fatal dose of a fresh normal suspension of the organism, no protective power was exhibited.

A similar property was seen to be possessed by the serum of guinea-pigs immune from double the fatal intraperitoneal dose of living vibrios. Thus, for example, the serum from such an immune guinea-pig when injected into the peritoneal cavity of each of two susceptible guinea-pigs in the dose of 1 cubic centimetre protected one of them against the simultaneous intraperitoneal injection of a little more than the fatal dose of living culture, and postponed the death of the other for three days. In all cases the control animals inoculated with the same dose of living culture, but which did not receive the serum, died after the proper interval with the characteristic lesions. On other controls that received only the serum no effect was produced.

I failed to observe with this serum the peculiar microscopic phenomenon, described by Pfeiffer and Vagedes,[1] that is seen to occur when the cholera spirillum is studied in a hanging drop made with the serum of very highly immunized animals. The failure to observe this reaction is probably due to the fact that my animals had been brought to only a very low degree of immunity.

Because of the many points of resemblance between the organism here described and Vibrio Metchnikovi, an effort was made to determine if pigeons rendered immune from Vibrio Schuylkilliensis were also immune from Vibrio Metchnikovi, and *vice versa*. The results show that such a reciprocal immunity occurs and persists for at least a week or ten days. It must be remembered, however, that this does not of necessity signify identity, for it will be borne in mind that Issaeff and Ivanoff,[2] in their studies upon the immunity induced by Vibrio Ivanoff, found that animals protected against it were also protected against Vibrio choleræ Asiaticæ. Nevertheless, the points of resemblance between Vibrio Schuylkilliensis and Vibrio Metchnikovi are so

[1] Pfeiffer and Vagedes: Centralbl. f. Bakteriol. u. Parasitenk., Bd. xix. p. 385.
[2] Issaeff and Ivanoff: Zeitschr. f. Hyg. v. Infektionskrankh., Bd. xvii. p. 117.

conspicuous and the points of difference so slight, being only quantitative, that I am constrained to consider them as very closely allied, if not identical. I cannot at this time, however, consider them identical, for the reason given—namely, that it has thus far been impossible to increase the virulence of Vibrio Schuylkilliensis for pigeons to anything approaching the degree possessed by Vibrio Metchnikovi. In experiments with the latter organism I have found that very much attenuated cultures may quickly be brought to such a degree of virulence, by successive passage through pigeons, that the characteristic pathogenic powers will be exhibited when very small doses are used, such, for instance, as a minute particle on the point of a straight needle; this, when rubbed into a superficial wound of the pectoral muscle of a pigeon, causes death in about twelve hours with general invasion of the body by the organisms. (Pfeiffer makes a similar statement concerning his experience with this organism.)

Whether the organism under consideration is or is not a modification of Vibrio Metchnikovi, or is or is not identical with either of the hitherto-described species, is of but little moment for the present. The important point to be borne in mind is, that as obtained from the waters in which it was found it was so anomalous in its pathogenic peculiarities as to make it impossible to do more than include it in the general group of suspicious vibrios. Its comparatively low infective properties for pigeons, its characteristic reaction by intraperitoneal inoculation of guinea-pigs, and the majority of its cultural and morphological peculiarities might readily lead one to mistake it for an organism of much more important significance, especially if surrounding circumstances, such as the presence of suspicious intestinal troubles, would seem to justify such an opinion.

In the light of this observation I think we can safely say that there exist pathogenic spirilla, sufficiently similar to the cholera spirillum to justify their being classified as suspicious, which manifestly have nothing to do with the disease cholera. I cannot avoid the conclusion that the discovery of this organism in the water of a locality absolutely free from suspicion, in so far as Asiatic cholera is concerned, serves as an additional refutation of the opinion that the cholera spirillum and the majority of the forms that simulate it are but variations of one and the same species. There may be a striking family likeness, but one produces cholera while the others do not; a distinction that, in the

present state of our knowledge, cannot be ignored, no matter what may be the outcome of subsequent studies of the causes underlying variability of species.

So far as I am aware, this is the first suspicious pathogenic spirillum that has been detected in the surface waters of this country. This is probably not due to their rarity or to their being peculiar to the waters of particular localities, but rather to the fact that few systematic efforts have been made to discover them.

If they are generally present it is important for us to know it, for in the event of an outbreak of cholera or of suspicious intestinal troubles of other nature they would undoubtedly prove the cause of endless confusion and false interpretations were their presence unsuspected.

It is with the hope of awakening an interest in the subject among American bacteriologists and of obtaining general data on this important subject that this contribution is made.

Explanation of Plates.

All of the figures are photomicrographs of the Vibrio Schuylkilliensis. For Figs I. and II. I am indebted to Dr. Charles L. Leonard, of the University of Pennsylvania.

Plate I.

Fig. 1.—Vibrio Schuylkilliensis. Normal forms as seen in fresh cultures on gelatin. × 1000 diameters.

Fig. 2.—Involution forms. From potato-culture forty-eight hours old. × 1000 diameters.

Fig. 3.—Colonies in gelatin plate after twenty-four hours' growth at 18° to 20° C. × 100 diameters.

Fig. 4.—Colonies in gelatin plate after forty-eight hours' growth at 18° to 20° C. × 100 diameters.

Plate II.

Fig. 5.—Colony in gelatin after about fifty hours' growth at 18° to 20° C. × 100 diameters.

Fig. 6.—Colony in gelatin after about seventy hours at 18° to 20° C. × 100 diameters.

Fig. 7.—Colony in gelatin after about seventy hours at 18° to 20° C. × 100 diameters.

Fig. 8.—Colony in gelatin after about seventy hours at 18° to 20° C. × 100 diameters.

Plate III.

Fig. 9.—Colony in gelatin after three days and a half. At two days to two days and a half this colony showed distinct concentric markings. Temperature, 18° C. × 100 diameters.

Fig. 10.—Edge of single colony in gelatin after two days and a half at 18° C. × 100 diameters

Fig. 11.—Stab-cultures in gelatin at 18° to 20° C.: *a*, after four days; *b*, after seven days; *c*, after seventeen to eighteen days. Approximately natural size.

PLATE I.

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

PLATE II.

Fig. 5.

Fig. 6.

Fig. 7.

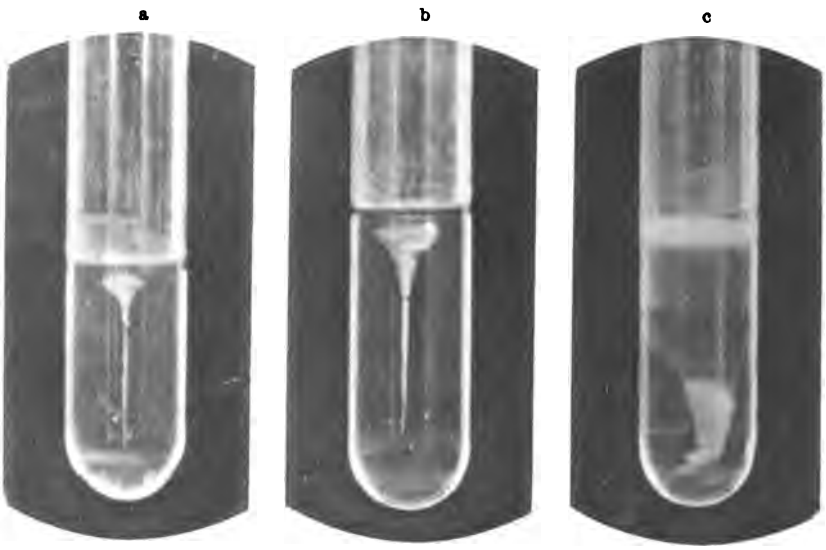
Fig. 8.

PLATE III.

FIG. 9.

FIG. 10.

FIG. 11.



DISCUSSION.

DR. VAUGHAN: This paper of Dr. Abbott's is very interesting. I do not think this pathogenic spirillum can be very widely distributed in the country. Since 1888 I have examined about 400 samples of suspicious water. I have tested the virulence of the bacteria in these waters, and while, of course, I have not been especially looking for spirilla, I have never found a pathogenic spirillum in the waters I have examined. All the pathogenic germs I have found have been bacilli. These waters have come from as far east as Connecticut, as far west as Colorado, as far south as Mississippi, and as far north as Dakota. Many of these waters, however, were well waters and not surface waters.

DR. THEOBALD SMITH: As far back as 1886 I found spirillum Finkler-Prior in this country. I isolated it from lungs affected with contagious pleuro-pneumonia. The lung came from West Virginia packed in ice. Whether the spirillum was in the lung or in the water I am not sure. That was, I think, the first case of a pathogenic spirillum described in this country.

DR. H. M. LYMAN: I would like to ask Dr. Abbott if he has extended his examination to the mouth of the Delaware River in order to ascertain whether these spirilla are found in salt as well as fresh water?

DR. BOLTON: I would like to know if Dr. Abbott applied Pfeiffer's test to this organism?

DR. ABBOTT: As stated, the object of this contribution is to direct more attention to this important subject, and to elicit just such evidence as that to which Dr. Vaughan has made reference.

I am not aware of the method employed by Dr. Vaughan in examining the waters submitted to him, so that I cannot discuss the reason for his negative results; I can only say, however, that the spiral forms are not detected, except by the merest accident, by the ordinary methods of bacteriological analysis. They are detected, when present, with comparative ease, by Koch's modification of the method of Schottelius referred to in my paper. The importance of the method used is illustrated by an experience that we had in our laboratory: In Dr. J. H. Wright's studies of the Schuylkill waters, covering ten months, not a colony of the colon group of bacilli was obtained by the ordinary plate method; whereas, with the subsequent application of the method used for detecting the spirilla, colon colonies are present in a large proportion of the samples examined.

As stated, I have not made a systematic study of the water at different points of the river or at different seasons, so that I cannot answer the question of Dr. Lyman.

In reply to Dr. Bolton I can only say that I have written to Professor

P.eiffer for a sample of his specific cholera serum. Until it arrives this point must remain open, though I feel no doubt that the organism under consideration will give a negative reaction with this serum.

DR. STERNBERG: Will it correspond with the Vibrio Metchnikovi in producing septicæmia?

DR. ABBOTT: When injected into the pectoral muscle of a pigeon it causes death. At autopsy there are usually spirilla in the blood, though few in numbers. After passing the organism through 20 pigeons successively I have not succeeded in increasing its virulence to a degree anything like that of the typical vibrio Metchnikovi. The blood of the animals is never as rich in bacteria as it is when death has resulted from inoculation with vibrio Metchnikovi.

THE INFLUENCE OF ACUTE ALCOHOLISM ON THE NORMAL VITAL RESISTANCE OF RABBITS TO INFECTION.

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(*From the Laboratory of Hygiene, University of Pennsylvania*)

DURING the past six months a portion of the time at my disposal has been occupied with experiments the results of which I propose to embody in this contribution. These studies were made in the Laboratory of Hygiene of the University of Pennsylvania under the auspices of the Committee of Fifty to Investigate the Alcohol Question, who generously placed at my disposal the funds necessary to defray the expenses of the work.

In the distribution of the several subdivisions of the general question relating to the influence of alcohol upon the physical and moral well-being of those who use it as a beverage, the Committee has seen proper to assign to me for experimental solution one of the most interesting and important phases of the subject—viz., that concerning the influence of alcoholism, acute and chronic, upon the normal vital resistance of animals to various forms of infection. In undertaking the work a general scheme of procedure was drawn up that seemed to meet most of the requirements of the problem, but as I now review it I find that it has been possible, in the time at my disposal, to cover only a limited portion of the ground included in this scheme.

The lines along which it was proposed to conduct these investigations are as follows:

1. Determine if the normal vital resistance of animals to infection by the common pathogenic bacteria is demonstrably influenced by either acute or chronic alcoholism, induced through the use of known amounts of pure ethyl-alcohol.

2. If any or no effect is observed, determine if the same holds good for animals under the influence of the commoner alcoholic beverages, as beer, wine, whiskey, cordials, etc.

3. Determine if through either acute or chronic alcoholism the germicidal properties of the serum of the blood of animals is materially altered. If so, determine, if possible, the nature of this alteration.

Thus far the work has borne upon the question concerning the influence of acute alcoholism upon the resistance of rabbits to infection by the pyogenic cocci—*i. e.*, the streptococcus pyogenes (erysipelatis) and the staphylococcus pyogenes aureus—and by the bacillus coli communis, and the results are in many ways sufficiently instructive to warrant their report at this time.

A difficulty that arose at the outset was in procuring cultures of pathogenic organisms of suitably diminished virulence without their being at the same time totally devoid of this property. As experience has taught us to expect certain deviations from the usual course of infection when normal animals are inoculated with attenuated cultures, such, for instance, as prolongation of the period of incubation and modification of the pathological lesions, the problem under consideration seemed to be in part most easy of solution through a comparison of results obtained by the use of such cultures on groups of alcoholized and non-alcoholized animals. Should such modifications occur in the normal animals, as would be anticipated, and an infection not differing from that produced by fully virulent cultures occur in the alcoholized animals, the difference could reasonably be referred to a reduction of vital resistance brought about by the alcohol administered.

To meet the requirements it would perhaps have been best to have employed cultures of organisms that were diminished in virulence to definite degrees of attenuation, such, for instance, as the bacillus anthracis attenuated to the degree of virulence represented by its primary and secondary vaccines. As such material was not at my disposal, however, cultures of another sort were used—namely, those that were of a low degree of virulence without this degree being definitely determined.

Again, cultures of organisms were employed the pathogenic powers of which are usually irregular and uncertain, while in still other tests

an effort was made to detect a difference between alcoholized and non-alcoholized animals when inoculated with virulent material, but in very small doses, hoping in this way to demonstrate, by a difference in the period of incubation, a difference of resistance in the animals composing the two groups.

The experiments were made with cultures of streptococcus pyogenes of a low degree of virulence, with normal bacillus coli communis, and with virulent staphylococcus pyogenes aureus, and, as the results to be reported show, with very diverse consequences.

Another difficulty was encountered in regulating the dose of alcohol. The intention was to have the animals daily in a state of intoxication, but it is not easy to decide just when this stage is reached, as the only certain indication of it is inco-ordination of muscular movement. It frequently occurred that when alcohol was given to this stage the direct effect of the drug was such as to gravely imperil the life of the animal, and in a certain number of instances the animals did not rally from even so few as one or two such administrations. If the dose were diminished, then one could often not be sure that the rabbit was intoxicated.

On the other hand, one encounters occasionally an individual on whom alcoholism to intoxication has apparently no effect upon the general health, and may be prolonged over relatively long periods. One of my animals, for instance, received daily doses of alcohol ranging from 5 to 15 cubic centimetres for one hundred and fourteen days. Its weight at the beginning was 1330 grammes, and at the end 1350 grammes, while during the interval its weight had been as high as 1520 grammes and as low as 1090 grammes. It died under the administration of 15 grammes daily with macroscopic lesions of only the gastric mucous membrane. I believe that the studies upon the effects of smaller, non-intoxicating doses of alcohol will demonstrate the possibility of continuing the administration of the drug over practically an indefinite period, quite to the stage of chronic alcoholism, in a fair proportion of the animals treated in this way.

The individual susceptibility of different animals to the physiological action of alcohol differed in such a way as to require at the beginning a special dose for each individual. It is impossible to maintain throughout a constant relation between body-weight and dose necessary to produce the desired effects. For instance, it cannot be

said if 5 cubic centimetres of alcohol produce intoxication in a rabbit of 1000 grammes weight, that necessarily 10 cubic centimetres will have the like effect in the next rabbit of 2000 grammes weight. The dose can only be determined by experiment.

It frequently occurred that, when the necessary dose had been determined, its continuous administration over several or more days resulted in very rapid and marked loss in body-weight, an indication of the greatest importance, meaning, that if the alcohol be continued the animal is practically certain to die. Under these circumstances it becomes necessary to either diminish the dose or cease the administration entirely for a time, until the loss of weight is partially or completely recovered. During the interval of rest, as it may be called, the animal is, of course, not daily intoxicated, and while the records of these experiments refer to animals "daily under the influence of alcohol to the stage of intoxication," it will be borne in mind that with many of these animals such periods of rest, varying in duration, were more or less frequently necessary.

As it was impossible to induce the rabbits to take alcohol voluntarily, either with the food or otherwise, it became necessary to administer it through a soft-rubber catheter passed down the œsophagus into the stomach, and though this was done as gently as possible, the irritation resulting from the repeated passage of the catheter, together with the depressing influence of the drug, was accompanied in a number of instances by intercurrent infections which, from their character and location, I think can be reasonably traced to insignificant wounds of the mucous surface of the œsophagus made when the alcohol was administered.

In only two instances was death positively the result of inspiration of alcohol into the air-passages at the time of operation. When such an accident occurs death is practically instantaneous.

The most common macroscopic effect of the direct action of the alcohol was erosion and inflammation of the mucous membrane of the stomach, a condition that was unfortunately present in quite a number of my animals, and which complicated matters in such a way as to vitiate considerably the results of the experiments.

When the necessary dose of alcohol was determined, it was always given mixed with an equal quantity of distilled water.

The dose necessary to positively produce intoxication ranged from

5 cubic centimetres to 15 cubic centimetres of pure ethyl-alcohol, though the usual dose in rabbits of from 1500 to 1800 grammes weight was from 7.5 cubic centimetres to 10 cubic centimetres, doses which, if taken by a man of one hundred and fifty pounds weight, would be roughly equivalent to from two-thirds to five-sixths of a pint of absolute alcohol. Notwithstanding this apparently very large amount, animals have repeatedly been encountered on which from 10 to 12, and even 15 cubic centimetres had no visible influence, though the continuance of these doses in many instances was followed by death associated with grave lesions of the gastric mucous membrane.

While rabbits offer conditions in a way favorable to experiments of this character, they are so liable to intercurrent bacterial and protozoal infections as to lead to many irregularities when large numbers of them are used. In the course of this work a number of experiments have been seriously vitiated by reason of such complications. The general plan followed in these experiments was to employ groups of equal numbers of animals. All were inoculated in the same way, then to one group alcohol was given, while to the other no alcohol was administered. They were all then kept under the same conditions of food, etc. Each animal was weighed in the morning before it was fed. In one or two cases the number of "controls" was fewer than that of the alcohol group. Control animals receiving only alcohol were not introduced into each experiment, as the necessary data on this point could always be had by reference to the records of preceding experiments in which the different effects of the drug on different animals were recorded.

Without going further into the particulars, it will suffice to tabulate the details and briefly summarize the results of each experiment as follows:

EXPERIMENT I. Summary of the results of the intravenous inoculation of rabbits receiving daily doses of alcohol to the stage of intoxication, with bouillon cultures of streptococcus pyogenes obtained from a phlegmonous inflammation in man:

Of eleven rabbits inoculated intravenously with varying amounts of streptococcus pyogenes, six received daily doses of alcohol for different lengths of time. The remaining five of this group received no alcohol. In addition, two rabbits received only daily doses of alcohol. Of the six inoculated animals that received alcohol, all died after

marked loss of weight and all exhibited lesions referable to the inoculation. One revealed a condition of the liver probably the result of the action of the alcohol.

Of the five inoculated animals to which no alcohol was given, one died, one was killed, and three recovered.

The one that died presented no lesions referable to the inoculation. Cultures revealed the presence of streptococci in the liver mixed with another organism, while the other internal organs were sterile.

The animal that was killed presented no lesions of importance, and its blood and internal organs were found by culture-test to be sterile.

Each of the three remaining animals suffered from temporary erysipelas of the ear at the site of needle-puncture. They recovered from this, and at the end of one hundred and twenty days were apparently in good condition, one having gained 330 grammes, the other 110 grammes, and the other 270 grammes in weight.

Of the two animals that were not inoculated, but which received alcohol daily, one died after one hundred and fourteen days with a condition of the gastric mucous membrane referable to the alcohol, the other after thirty-four days with no macroscopic lesions to account for death.

EXPERIMENT II. Summary of the results of intravenous inoculation of rabbits, receiving intoxicating doses of alcohol daily, with suspensions of streptococcus pyogenes:

The eighteen animals employed in this experiment were divided into four groups and treated as follows:

Four receiving intoxicating doses of ethyl-alcohol for five days and were then inoculated intravenously with 0.5 cubic centimetre of a suspension of streptococcus pyogenes.

Five received intoxicating doses of methyl-alcohol for five days and were then similarly inoculated.

The alcohol was continued in both groups after inoculation until death.

Five received, in addition to the inoculation, daily doses of distilled water, injected into the stomach in the same manner as was the alcohol in the other animals, for fifteen days. After this alcohol was given to two of them—to one for two days, to the other for six days—while the remaining three got nothing from the fifteenth day.

Four were simply inoculated. One of this group received a single dose of alcohol.

The nine latter animals served as controls.

RESULTS. Of nine inoculated animals to which alcohol was given, seven died with suppurative lesions.

Of nine inoculated animals that received no alcohol until after the fifteeenth day, when alcohol was given to two, five died, three were killed, and one was observed for fifty-two days. In only three of the nine were suppurative lesions detected at autopsy.

Of the seven alcohol animals that died, five presented lesions at autopsy that could be attributed to the action of the alcohol.

EXPERIMENT III. Summary of the results of intravenous inoculation of rabbits receiving alcohol daily to the stage of intoxication, with suspensions of bacillus coli communis from human feces:

Of five rabbits, each of which was inoculated with 1 cubic centimetre of a suspension in bouillon of bacillus coli communis, and all of which had been receiving alcohol to the stage of intoxication daily for five days, four died in from eighteen to twenty hours and one in eighteen days after inoculation.

None presented lesions referable to the inoculation. One revealed a condition of the gastric mucous membrane that evidently resulted from the direct action of the alcohol. Bacillus coli communis was obtained in cultures from the internal organs of all.

Five rabbits, each of which had been receiving alcohol in doses ranging from 2.5 to 15 cubic centimetres daily for thirty-one days, were inoculated intravenously with the same material in the same amount that was employed in the preceding group.

One died within twenty-four hours after the inoculation.

Four died in from forty-three to fifty-five days after the inoculation.

Three presented at autopsy lesions referable to the inoculation—viz., the condition of the liver, gall-bladder, and bile described by Blachstein.[1]

Two presented no lesions attributable to the inoculation.

Two showed a condition of the liver that may possibly have resulted

[1] Blachstein: Intravenous Inoculation of Rabbits with the Bacillus Coli Communis and the Bacillus Typhi Abdominalis. Bulletin of the Johns Hopkins Hospital, vol. ii. No. 14, July, 1891.

from the prolonged action of the alcohol, while in the remaining three no results of the alcohol were evident.

Two control animals that were inoculated in the same manner with the same material, but which received no alcohol, were alive on the seventy-ninth day after inoculation. By the sixtieth day one had gained 230 grammes in weight, while the other, though apparently well, had lost 200 grammes in weight.

EXPERIMENT IV. Summary of the results of inoculation of alcoholized animals with suspensions of bacillus coli communis:

Three animals received intravenous inoculation of 0.5 cubic centimetre of a suspension of bacillus coli. Immediately afterward the administration of alcohol was begun. One died during the night and one on the day following the inoculation. Bacillus coli was found by cultures in the internal organs of both. The third died eight days after inoculation with no characteristic lesions and no colon bacilli in the internal organs. The mucous membrane of the stomach was eroded and there was a fibrino-purulent pericarditis and pleuritis, evidently the result of an intercurrent infection, probably induced by the repeated passage of the catheter along the œsophagus.

Three other rabbits that had been getting alcohol for four days were inoculated in the same manner as the preceding. Two died on the ninth day and one on the eighteenth day following inoculation.

In one, dead on the ninth day, were the characteristic lesions described by Blachstein. There was also present a condition of the stomach that was manifestly the result of the action of the alcohol.

Of the remaining two, in one death ensued from an intercurrent infection, while in the other death was the result of an intestinal intussusception. This latter animal presented erosion of the gastric mucous membrane that was evidently the result of the action of the alcohol.

In both animals that died on the ninth day colon bacilli were present in cultures from the internal organs, while in the one dead on the eighteenth day the blood and internal organs were sterile.

Three control animals were alive and apparently well on the forty-sixth day. One had gained 50 grammes, the other 280 grammes, while the third had lost 120 grammes in weight.

In short, of six alcoholized rabbits inoculated with colon bacilli, all died. One presented characteristic lesions at autopsy. Of three non-alcoholized control animals, none died.

EXPERIMENT V. Results of intravenous inoculation of rabbits receiving alcohol, with cultures of staphylococcus pyogenes aureus:

In this experiment the first inoculation was without effect, and the animals were inoculated a second time after an interval of seven days. Four animals were employed—viz., two alcoholized and two controls. The alcoholized animals died in fourteen and two days, respectively, after the inoculation. Both presented lesions referable to the inoculation and neither showed conditions due to the direct action of the alcohol. One control animal died in four days after the first inoculation, while the second died in six days after the second inoculation. To this latter animal alcohol was administered from the time of the second inoculation. Both presented lesions referable to the inoculation, and the one that got alcohol presented also conditions due to the direct action of the alcohol.

This experiment does not demonstrate any material difference between the alcoholized and the non-alcoholized animals as regards their susceptibility to this form of infection.

EXPERIMENT VI. Subcutaneous inoculation of alcoholized animals with cultures of staphylococcus pyogenes aureus:

There were four animals in this group, two alcoholized and two controls. In all except one, an alcoholized rabbit, the subcutaneous inoculation was without effect up to the seventh day. On the seventh day the three remaining animals were inoculated again, but this time intravenously.

RESULTS. One alcoholized animal died in three days after the subcutaneous inoculation. Death was due to pseudo-tuberculosis of the lungs. There was only a trifling area of suppuration at the seat of inoculation. The other alcoholized rabbit died four days after the intravenous inoculation and presented the usual condition of widespread miliary-abscess formation. Both control animals died after the intravenous inoculation—the one in seven days, the other in twenty-four hours. The former presented lesions characteristic of the inoculation, while the latter presented no macroscopic lesions at all at autopsy. The former control animal had been given alcohol since the date of its second intravenous inoculation. At autopsy it presented lesions referable to the direct action of the alcohol.

EXPERIMENT VII. Intraperitoneal inoculation of alcoholized animals with cultures of staphylococcus pyogenes aureus:

Four animals were employed; two received alcohol and two served as controls.

The animals that exhibited no effects of the intraperitoneal inoculation at the end of a week were reinoculated with the same material, but this time the inoculation was intravenous.

One alcoholized animal died the day following the intraperitoneal inoculation, the other two days after the intravenous inoculation.

In neither were lesions detected that could account for death, or be positively referred to either the inoculation or the alcohol.

Both control animals recovered from the intraperitoneal inoculation and at the end of a week were inoculated intravenously.

One died two days after this latter inoculation and presented neither mycotic nor alcoholic lesions, death being due to rupture of the gravid uterus, while the other died nine days after intravenous inoculation with abscesses in myocardium and kidneys.

EXPERIMENT VIII. Intravenous inoculation of alcoholized rabbits with bouillon-cultures of staphylococcus pyogenes aureus:

Of the six inoculated animals to which alcohol was given, three died in less than twenty-four hours and three in from forty-eight to seventy-two hours after inoculation. In three, lesions were present that could positively be referred to the inoculation, and in one the condition was doubtful. In two no such lesions could be found.

In five of the six animals a condition of the mucous membrane of the stomach was found that was evidently the result of the direct action of the alcohol.

Of the six inoculated animals that did not get alcohol three died in less than twenty-four hours, two after five and twelve days, respectively, while the remaining animal was apparently well at the end of forty-three days.

Three of these animals presented lesions that resulted from the inoculation: in one the lesion was doubtful, in one no lesions were detected, and the sixth is still alive.

This experiment demonstrates a slight, though not very important or striking, difference between the course of infection in the two groups.

EXPERIMENT IX. Subcutaneous inoculation of alcoholized rabbits with cultures of staphylococcus pyogenes aureus:

Of the six inoculated animals to which alcohol was given, one died

during the night following the inoculation; the remaining five died in from five to fifteen days later.

Two of these animals presented no lesions referable to the inoculation, one presented an extensive local lesion, and three presented a lesion of the pleuræ and pericardium of doubtful significance. This condition was identical in the three animals and consisted of a fibrino-purulent inflammation of practically all the serous surfaces within the thoracic cavity. Cultures from this lesion revealed the presence of a staphylococcus that grew feebly, producing but a very faint, barely perceptible, cream color, and in general gave the impression that it might be an attenuated or enfeebled culture of staphylococcus aureus. It was not studied in detail.

The animals in which this lesion was found died in five, fifteen, and fifteen days, respectively.

The three control animals used in this experiment manifested no ill effect of the treatment. They were alive and well at the end of forty-six days after inoculation.

In none of the six animals that received alcohol was there any macroscopic evidence of the action of the alcohol on the tissues.

EXPERIMENT X. Intravenous inoculation of alcoholized rabbits with staphylococcus pyogenes aureus attenuated (?) by exposure to chloroform:

Four animals were used in this experiment.

Of the two inoculated animals to which alcohol was given one died on the fifth, the other on the second day following the inoculation. One presented a lesion of the kidney positively referable to the inoculation, the other a condition of the peritoneum that probably, though not certainly, resulted from the treatment to which the animal had been subjected.

Both of these animals presented extensive erosions of the gastric mucous membrane that were manifestly the result of the direct action of the alcohol.

Neither of the two control animals evinced any ill effects from the inoculation; both gained in weight, and at the end of twenty-eight days were eliminated from the experiment as not likely to manifest evidences of infection.

TABULATED DETAILS OF FOREGOING EXPERIMENTS.—EXPERIMENT I.

Table showing the results of intravenous inoculation of rabbits that were receiving daily doses of ethyl-alcohol to the stage of intoxication, with bouillon cultures and with suspensions of the streptococcus pyogenes obtained from a phlegmonous inflammation of the foot of a man.

Rabbits.	No. of days observed	Total amount of alcohol received. C.c.	Daily dose of alcohol. C.c.	Interval between the beginning of alcohol and time of inoculation.	Weight in grammes. Beginning.	Weight in grammes. End.	Lesions referable to inoculations. +=present. 0=absent.	Lesions referable to the alcohol. +=pres. 0=abs.	Results and remarks.
1	41	250	5–10	36 days; was then inoculated with 1 c.c of bouillon culture of streptococcus intravenously.	1190	910	+ General infection.	+ (?) (Liver.)	Died six days after inoculation; liver very yellow and friable; contained large numbers of streptococci; many of the capillaries quite filled with them; streptococci also present in pure culture in blood, kidney, and bone-marrow; no abscesses detected.
2	40	240	5–7.5	35 days; inoculation same as that of No. 1.	1210	880	+ Miliary abscesses in muscles.	0	Died on sixth day after inoculation; numerous miliary abscesses in muscles along the spine; no abscesses in myocardium or kidneys. *Cultures:* Streptococci in pure culture in muscle abscess, blood, liver, kidney, and spleen.
3	49	297.5	5–7.5	45 days; intravenous inoculation of bouillon culture of streptococcus 24 hours old.	1280	960	+ Miliary abscesses in muscles.	0	Died on fifth day after inoculation; miliary abscesses throughout the voluntary musculature. Abscesses in myocardium; pale areas, but no abscesses in kidneys; spleen dark and congested. *Cultures:* Streptococci in pure culture and in large numbers in muscle abscesses, blood, liver, spleen, and kidney.
4	47	282.5	5–7.5	45 days; inoculation same as that of No. 3.	1200	1040	+ Abscesses(?) in myocardium; general infection.	0	Died on third day after inoculation. No abscesses in muscles; several pale points in myocardium; these contained streptococci in large numbers on microscopic examination. *Cultures:* Streptococci in pure culture from pale points in heart, from blood, liver, spleen, kidney, and peritoneal cavity.
5	16	145	7.5–10	Inoculated three times. Intervals: First, two days; second, four days; third, seven days. Last inoculation (fatal) was 0.8 c.c of a bouillon culture of streptococcus intravenously.	1740	1290	+ Miliary abscesses in muscles.	0	Animal had two subcutaneous inoculations, first two days and second four days after beginning of alcohol; seven days after beginning of alcohol it received an intravenous injection of 0.8 c.c. of a bouillon culture of streptococcus pyogenes. Died nine days after last inoculation. Sites of subcutaneous inoculations sterile. As result of intravenous inoculation the voluntary muscles were everywhere studded with miliary abscesses; similar abscesses in diaphragm; none in internal organs. *Cultures* from abscesses in muscles and from blood show streptococci in pure culture.
6	3	30	10	Both given at same time. Same inoculations as those for No. 5.	1910	1740	+ Miliary abscesses in muscles.	0	Died in afternoon of second day after inoculation. Miliary abscesses throughout voluntary muscles, especially those of thorax; spleen very large, almost black in color, measured 6.5 cm. long, 2 cm. wide, and 1.5 cm. thick; numerous abscesses in myocardium. *Cultures* and cover-slips revealed streptococci in muscle abscesses, liver, spleen, blood, and kidney.

Control animals.

A	114	845	5–15	Not inoculated.	1330	1350	.....	+ Mucous membrane of stomach.	The daily dose of 15 c.c. was begun eight days before death, after the animal had been getting 10 c.c. daily for thirty-seven preceding days. *Autopsy* revealed macroscopic lesions only in the stomach. The walls were thickened and œdematous, in some places thin. There was widespread erosion and necrosis of the mucous membrane.
B	34	147.5	5–10	Not inoculated.	1030	600	.....	0	The animal was markedly susceptible to alcohol. At autopsy, no macroscopic lesions to account for death were found.
C[1]	120	No alcohol.	.....	No alcohol; inoculated at same time and in same way as No. 1.	.....	.....	+ Erysipelas of ear about site of operation.	.....	In three weeks after inoculation this animal was well, having had a local erysipelas of ear at point of puncture of needle. After four months it had gained 330 grammes in weight, and was not observed further.
D[2]	120	No alcohol.	.....	No alcohol; inoculated at same time and in same way as No. 2.	.....	.....	+ Temporary erysipelas of ear at site of operation.	.....	After about three weeks the animal was well of its local erysipelas in ear; it had recovered its lost weight, and was apparently in good condition. At end of four months it had gained 110 grammes in weight; observation discontinued.
E[3]	120	No alcohol.	.....	No alcohol; inoculated at same time and in same way as No. 3.	.....	.....	+ Temporary erysipelas of ear.	.....	Temporary redness and swelling of ear at site of operation. At end of four months had gained 270 grammes; observation discontinued.
F[4]	16	No alcohol.	.....	No alcohol; inoculated at same time and in same way as No. 4.	1220	800	+	.....	Died after sixteen days. For some time had had profuse watery discharge from nostrils and mouth; this began on fourth day after inoculation; no lesions of importance found at autopsy. *Cultures:* Blood, pure culture of streptococci; liver, streptococci, with a large micrococcus; lung, kidney, and spleen sterile.
G[5]	15	No alcohol.	.....	No alcohol; inoculated at same time and in same way as No. 5.	1410	1590	+ Circumscribed pus formations at sites of subcutaneous inoculations.	.....	Animal killed on fifteenth day—*i. e.*, nine days after its last (intravenous) inoculation; no miliary abscesses in muscles and no lesions of internal organs found at autopsy; circumscribed pus formations in stages of healing at both sites of subcutaneous inoculation. *Cultures* from sites of subcutaneous inoculation and internal organs showed them to be sterile.

[1] Control for No. 1. [2] Control for No. 2 and No. 6. [3] Control for No. 3. [4] Control for No. 4. [5] Control for No. 5.

EXPERIMENT II.

Table showing results of intravenous inoculation of rabbits, that were receiving daily doses of alcohol to the stage of intoxication, with suspensions of streptococcus pyogenes.

Ethyl-alcohol.

Rabbits.	No. of days observed.	Total amount of alcohol received. Cc.	Daily dose of alcohol. C.c.	Interval between the beginning of alcohol and time of inoculation.	Weight in grammes.		Lesions referable to inoculations. +=present. 0=absent.	Lesions referable to the alcohol. +=present. 0=absent.	Results and remarks.
					Beginning.	End.			
7	13	142 5	7.5-15	5 days; intravenous injection of 0.5 c.c. of a suspension of streptococcus pyogenes.	2010	1650	0	0	Died eight days after inoculation. *Autopsy:* No lesions anywhere to be detected. No streptococci in cultures. Cultures all contain short oval bacillus. Evidently an intercurrent infection.
8	12	142.5	7.5-15	Same as No. 7.	1600	1350	+ Muscle abscesses.	+ (Stomach.)	Died seven days after inoculation. Abscess in muscles of both thighs; none in heart or kidneys. Mucous membrane of stomach very much eroded. *Cultures:* Streptococci in large numbers and in pure culture from blood, liver, kidney, and muscle abscess.
9	10	90	7.5-20	Same as No. 7.	1020	940	+ Streptococci in blood.	0	Died fourth day after inoculation. *Autopsy:* No abscesses anywhere in voluntary muscles; several diffuse pale areas in heart; numerous necrotic areas in liver. *Cultures* demonstrate a mixed infection; those from blood and kidney contain streptococci, those from the other organs contain a short oval bacillus.
10	12	132.5	7.5-15	Same as No. 7.	1860	1530	0	+ (Stomach.)	Died seven days after inoculation. *Autopsy:* Muscle abscesses not detected; liver contained coccidia nodules; kidneys presented several small cortical hemorrhages; mucous membrane of stomach inflamed and eroded. *Cultures:* No streptococci in cultures from blood, liver, spleen, kidneys, or peritoneal cavity. In all these tubes was a short oval bacillus.
11	...	.....	.....	.....	.....	.....	.....	....	Died on fourth day as result of alcohol. Had not been inoculated.
				Animals receiving commercial methyl alcohol.					
12	11	109	3-15	Same as No. 7.	1520	1260	+ Streptococcus septicæmia.	+ (Stomach.)	Died six days after inoculation. *Autopsy:* No muscle abscesses detected; liver studded with minute yellow points; mucous membrane of stomach very much reddened and eroded. *Cultures:* Streptococci in pure culture and in large numbers from blood, liver, and spleen.
13	7	54	3-10	Same as No. 7.	1200	1110	+ Streptococci in blood and internal organs.	0	Died on day after the inoculation. *Autopsy:* Liver contained psorosperm nodules in which streptococci in large numbers were found along with the characteristic parasite; kidneys pale; presented numerous minute cysts(?) over entire cortex. No abscesses anywhere. *Cultures:* Streptococci in pure culture and in large numbers from blood, liver, spleen, kidney, and peritoneal cavity.

14	12	109	3–15	Same as No. 7.	1000	1040	+ Abscess in muscle; streptococci in blood.	+ (Stomach.)	Died on seventh day after inoculation. *Autopsy:* A single abscess in muscle of the thigh was detected; slight excess of moisture in peritoneal cavity. No abscesses in myocardium or kidneys; a widespread area of erosion and inflammation of the mucous membrane of the stomach. *Cultures:* Streptococci in pure culture from spleen, liver, blood, kidney, and peritoneal cavity, they were present only in small numbers.
15	13	124	3–15	Same as No. 7.	1440	1420	+ Abscess on leg; streptococci in blood.	+ (Stomach.)	Died on eighth day after inoculation. *Autopsy:* On right leg, near axilla, between skin and muscles, was a circumscribed collection of pus of about the size of an almond; no miliary abscesses detected; several necrotic areas in liver; mucous membrane of stomach very red and eroded. This animal had a very acute and painful erysipelas of the ear for several days after inoculation. *Cultures:* Streptococci from blood, liver, and large abscess on leg.
16	8	46.5	3–10	Same as No. 7.	1240	1140	+ Muscle abscesses; streptococci in blood.	0	Died on second day after inoculation. *Autopsy:* Muscle abscesses in left thigh and in abdominal muscles; several abscesses in myocardium. *Cultures:* Streptococci from blood, liver, kidney, and muscle abscesses.

Control animals for this experiment. These animals were inoculated with the same material, at the same time, and in the same way as the ten preceding animals. For 15 days each received 20 c.c. of distilled water daily, injected into the stomach through a soft-rubber catheter.

17	21	20 c.c. of water daily for 15 days; alcohol then begun; in 6 d'ys 30 c.c. of alcohol given.	Water 20 c.c.; alcohol 10 c.c.; 3 days nothing	5 days from the beginning of water; inoculation same as preceding animals.	1010	860	0 (?) Condition of ear of this rabbit was evidently erysipelatous; unfortunately it was not examined at autopsy.	0	Died on fifteenth day after inoculation and on fifth day after alcohol was begun. *Autopsy:* For five days before death this animal has had very sore ear; it was thick, painful, and dependent; beyond a slight diminution in color, internal organs were normal; no lesions of muscles. *Cultures:* Blood, liver, and kidney sterile.
18	18	Water as in No. 17: one day nothing then got 10 c.c. alcohol on each 2 days.	Water 20 c.c.; alcohol 10 c.c.	Same as No. 17.	1130	1020	0	0	Died after second dose of alcohol—*i. e.*, thirteen days after inoculation. *Autopsy:* Neither recent nor remote suppurative lesions anywhere; small area of consolidation in left lung (inspiration pneumonia (?)); no bacteria found in cover slips from this. *Cultures:* Blood, liver, and kidneys sterile.

Rabbits.	No. of days observed	Total amount of alcohol received. C.c.	Daily dose of alcohol. C.c.	Interval between the beginning of alcohol and time of inoculation.	Weight in grammes. Beginning.	Weight in grammes. End.	Lesions referable to inoculations. +=present. 0=absent.	Lesions referable to the alcohol. +=present. 0=absent.	Results and remarks.
19	52	No alcohol; 20 c.c. water daily for 15 days; then got nothing for 37 days.	None.	5 days from the beginning of water.	1650	1500	0	.....	The weight of the animal ran up as high as 1710 and down as low as 1450 grammes while in the experiment: at the end of fifty-two days it was apparently well. Observation was discontinued. Showed no signs of sickness at any time.
20	16	Same as No. 19.	None.	Same as No. 19.	1120	1130	0	....	The weight of the animal went up to 1200 grammes in course of the experiment. It was killed on sixteenth day. *Autopsy:* Neither recent nor remote lesions anywhere; viscera apparently normal. *Cultures:* Blood, liver, spleen, and kidney sterile.
21	16	Same as No. 19.	None.	Same as No. 19.	1010	1030	0	.....	Weight was up to 1080 grammes at one time; killed on sixteenth day. *Autopsy:* No lesions of any kind anywhere; animal apparently normal. *Cultures:* Blood, liver, spleen, and kidney sterile.
Control animals getting nothing but the inoculation.									
22	11	.....	.....	No alcohol; inoculated on same date and in same way as preceding animals.	920	960	+ Abscesses; streptococcus septicæmia.	.....	Weight was up to 1030 during experiment; died five days after inoculation. *Autopsy:* Abscesses in voluntary muscles, in myocardium, and in right kidney; none in left kidney. *Cultures:* Streptococci in pure culture for blood, liver, spleen, kidney, and peritoneal cavity.
23	...	.....	.....	.....	.....	.....	.....	.....	Intercurrent infection before it was inoculated; excluded from the experiment.
24	25	.....	.....	Same as No. 22.	1320	1040	+ (?) Caseous gland in axilla.	.....	Died on twenty-fifth day; for some days before death there was profuse watery discharge from mouth and nose. *Autopsy:* A small caseous gland in right axilla; did not contain streptococci on microscopic examination; no other lesions noted beyond numerous minute petechiæ over cortex of kidneys. *Cultures:* Blood, liver, kidney, and peritoneal cavity sterile.
25	17	None until 16th day when 1 dose of 10 c.c. was given.		Same as No. 22.	1480	1250	+ Abscesses in muscle.	....	Died on second day after dose of alcohol—*i. e.*, on twelfth day after inoculation. *Autopsy:* Evidence of healed peritonitis; two large abscesses in left pectoral muscle; no abscesses in myocardium or kidneys; muscle abscesses apparently of long standing. *Cultures:* Streptococci from muscle abscesses; blood and kidney sterile.

26	16	No alcohol.	.....	No alcohol; inoculated on same date and in same way as preceding animals.	1490	1090	0	.....	Killed on sixteenth day after experiment was begun—*i. e.*, eleventh day after inoculation. *Autopsy:* Suppurative lesions, neither recent nor remote, were anywhere to be detected. *Cultures:* No streptococci in either the blood or the internal organs.

Experiment III.

Table showing the results of intravenous inoculation of rabbits, receiving daily doses of ethyl-alcohol to the stage of intoxication, with suspensions of bacillus coli communis from human feces.

27	6	55	7.5–10	5 days; intravenous injection of 1 c.c. of opaque suspension of bacillus coli 52 hrs. old.	1990	1970	0	+ (Stomach.)	Died about five hours after inoculation. *Autopsy:* Mucous membrane of stomach red; slight congestion of spleen and kidneys. *Cultures:* A few colonies of bacillus coli from liver; blood sterile.
28	6	55	7.5–10	Same as No. 27.	1890	1800	0	0	Found dead on morning following the injection. *Autopsy:* About 3 c.c. of reddish fluid in peritoneum. One or two dark areas in lungs; no other lesions. *Cultures:* Liver, blood, and peritoneal cavity gave bacillus coli in pure culture.
29	23	240	7.5–10	Same as No. 27.	1400	920	0	0	Died on twenty-third day—*i. e.*, eighteen days after inoculation. *Autopsy:* Pseudo-tuberculosis of apex of left lung; liver pale and tough; gall-bladder distended with dark-green bile. *Cultures:* Peritoneal cavity, five colonies, and bile, one colony; all were of bacillus coli.
30	6	55	7.5–10	Same as No. 27.	1690	1770	0	0	Found dead on morning following the inoculation; had evidently been dead some time, as post-mortem changes were in progress in all the organs. *Cultures:* Bacillus coli in pure culture from spleen, kidney, liver, and blood.
31	6	55	7.5–10	Same as No. 27.	1710	1470	0	0	Found dead on morning following the inoculation; post-mortem decomposition more or less advanced in all the viscera; no lesions discernible to naked eye. Pure cultures of bacillus coli obtained from blood, liver, spleen, kidney, and peritoneum.

The following animals were inoculated at the same time as the preceding, with the same amount of the same material. They differed from the preceding in having received alcohol daily for a much longer time before the inoculation.

32	32	112 5	2.5–7.5	31 days; same inoculation as above.	1130	1070	0	+(?) (Liver.)	This animal was so susceptible to alcohol that it could not be given regularly; found dead on morning following the inoculation. The only lesions found at autopsy were very pale liver and a circumscribed œdematous patch in the lung; colon bacilli in pure culture from blood, liver, spleen, and kidney.

Rabbits	No. of days observed	Total amount of alcohol received (c.c.)	Daily dose of alcohol (c.c.)	Interval between the beginning of alcohol and time of inoculation.	Weight in grammes. Beginning	Weight in grammes. End	Lesions referable to inoculations. O = present, absent.	Lesions referable to the alcohol. O = present, absent.	Results and remarks.
44	75	440	2.5–10	44 days, inoculated as above.	2000	1310	+ (Bile.)	O	Died on seventy-fifth day, *i. e.*, forty three days after inoculation. *Autopsy:* Moderate emaciation; liver so thickly studded with coccidia that nothing could be detected as to presence of other lesions; gall-bladder very much distended with clear, pale bile, in which floated amorphous flakes that could be seen through the walls of the organ; these consisted of leucocytes, epithelium, blood corpuscles, and bacteria. *Cultures:* Pure cultures of bacillus coli from bile and blood; cultures from liver contained colon bacilli with another bacillus (bacillus pyocyanus).
51	88	560	5–15	Same as No. 44	1560	1330	+ (Liver and bile.)	O	Died on eighty eighth day—*i. e.*, fifty-five days after inoculation. *Autopsy.* Slight emaciation; several irregular necroses in liver; very great distention of gall-bladder with clear, pale-greenish bile, in which was an amorphous sediment. *Cultures:* Colon bacilli in pure culture from the bile; liver and blood sterile.
56	87	560	2.5–15	Same as No. 44	1020	1220	O	+ (?) (Liver.)	Found dead on eighty-seventh day, *i. e.*, fifty-four days after inoculation. *Autopsy.* Liver large, tough, rough on its surface. On section, the open mouths of vessels are very conspicuous; gall-bladder filled with normal dark-green bile. *Cultures* demonstrated the blood, liver, and bile to be sterile.
60	84	547.5	2.5–10	Same as No. 33	1570	1070	+ (Liver and bile.)	O	Found dead on eighty-fourth day, *i. e.*, fifty-one days after inoculation. *Autopsy.* Both lungs in part affected with pseudo-tuberculosis; liver presented several irregular points of yellowish, superficial necroses; gall-bladder very large, distended with pale, clear bile, in which floated flakes of amorphous material; these could be seen through the walls of the distended organ. *Cultures:* Bacillus coli was obtained only from the bile; it was here in pure culture. From lungs bacillus pyocyanus (?) was obtained in pure culture.

Controls. Injected at same time as the others, but received no alcohol.

47	79			Injected as above	1400				Seventy nine days after inoculation this animal is still alive. Had gained by sixtieth day 200 grammes. Observation discontinued.
48	79			Injected as above	1640				Seventy nine days after inoculation the animal is alive, is apparently well, though it had lost 200 grammes in weight by sixtieth day.

EXPERIMENT IV.

Table giving the results of intravenous inoculation of rabbits, that were receiving daily doses of ethyl-alcohol to the stage of intoxication, with suspensions of bacillus coli communis from human feces.

39	11	90	10	Simultaneous; inoculated with 0.5 c.c. of a suspension of bacillus coli from agar-culture 24 hours old.	1540	1180	0	+ (Stomach.)	Died eight days after inoculation. Had been under observation for two days before any treatment was begun. *Autopsy:* Acute fibrino purulent pleuritis and pericarditis, due to intercurrent infection. Mucous membrane of stomach slightly eroded. No colon bacilli found in the cultures from blood and internal organs.
40	2	20	10	Same as No. 39.	1330	1190	0	0	Died on the day following inoculation. *Autopsy:* The only lesion found was an intussusception of the colon involving about 12 cm. of the length; it was very acutely congested, and evidently recent. *Cultures:* Blood sterile. Liver: a few colonies of bacillus coli.
41	1	10	10	Same as No. 39.	1760	.....	0	0	Died during night of the day on which it was inoculated. *Autopsy:* No macroscopic lesions. *Cultures:* Blood and liver contained large numbers of bacillus coli.
42	9	47 5	5–7.5	4 days; inoculated as above.	1180	950	0	+ (Stomach.)	Died on ninth day—*i. e.*, five days after inoculation. *Autopsy:* Liver presented several areas of superficial necrosis; gall-bladder filled with normal bile; a recent volvulus, with intussusception of small intestine; lymphatic apparatus of intestine enlarged, but not congested; mucous membrane of stomach eroded. *Cultures:* Colon bacilli in small numbers were obtained from liver, blood, bile, and spleen.
43	18	177.5	7.5–10	Same as No. 42.	2110	1780	0	0	Died on eighteenth day—*i. e.*, fourteen days after inoculation. *Autopsy:* Death ensued from intercurrent infection; no colon bacilli found in cultures.
44	9	87.5	7.5–10	Same as No. 42.	1520	1180	+ (Liver and bile.)	+ (Stomach.)	Died on ninth day—*i. e.*, five days after inoculation. *Autopsy:* Moderate emaciation; several irregular necroses in liver; gall-bladder distended with pale bile, in which amorphous flakes could be seen through the wall of the distended organ. Amorphous matter consisted of leucocytes, blood-corpuscles, and bacteria. Mucous membrane of stomach red and eroded. *Cultures:* Bacillus coli in blood, liver, bile, and spleen.

Controls. Inoculated in the same way, but with a larger dose of the same material as the preceding animals, but received no alcohol.

45	...	.....	.....	No alcohol; intravenous inoculation of 0.8 c.c. of the same suspension used in preceding rabbits of this experiment.	1560	.....	.....	.....	After forty-six days animal apparently well; weight, 1610 grammes.
46					1960	.....	.....	.....	After forty-six days animal apparently well; weight, 1840 grammes.
47					1510	.....	.....	.....	After forty-six days animal apparently well; weight, 1790 grammes.

EXPERIMENT V.

Table showing results of intravenous inoculation of rabbits, receiving daily doses of ethyl-alcohol to the stage of intoxication, with bouillon-cultures of staphylococcus pyogenes aureus.

Rabbits.	No. of days observed	Total amount of alcohol received. C.c.	Daily dose of alcohol. C.c.	Interval between the beginning of alcohol and time of inoculation.	Weight in grammes. Beginning.	Weight in grammes. End.	Lesions referable to inoculations. +=present. 0=absent.	Lesions referable to the alcohol. +=present. 0=absent.	Results and remarks.
48	24	200	10–15	3 days; intravenous inoculation of 0.3 c.c. of 24-hour bouillon-culture of staphylococcus aureus; after 7 days, similar injection of 0.5 c.c.	1900	1250	+ (Kidneys.)	0	Died on twenty-fourth day—*i. e.*, twenty-one days after first and fourteen days after second inoculation. *Autopsy:* Several old abscesses in the kidneys; gave appearance of being encapsulated; none in myocardium or voluntary muscles; widespread pseudo-tuberculosis of right lung. This is evidently the cause of death. *Cultures:* Staphylococcus aureus from kidney; blood, liver, and bile sterile; a long, slender bacillus growing in felt-like, tenacious colonies from the diseased lung.
49	12	110	10	Same as No. 48.	1360	1160	+ (Abscesses in kidneys and muscle.)	0	Died on twelfth day—*i. e.*, nine days after first and two days after second inoculation. *Autopsy:* One small abscess in voluntary muscles; numerous small abscesses in kidneys; none in myocardium. *Cultures:* Staphylococcus aureus in very small numbers from blood and kidney; peritoneum sterile.
							Controls.		
50	13	None until 7th day of experiment, then alcohol was begun; total amount, 50c.c.	10	Alcohol given simultaneously with the second inoculation; first inoculation as above; second inoculation on seventh day consisted of 0.5 c.c. of a bouillon culture of staphylococcus aureus intravenously.	2430	2250	+ (Abscesses in kidneys.)	+ (Stomach.)	Died on thirteenth day—*i. e.*, ten days after first and six days after second inoculation. *Autopsy:* Mucous membrane of stomach very much inflamed and eroded; several conglomerate abscesses in kidneys, none in myocardium or in voluntary muscles. *Cultures:* Staphylococcus aureus from kidney; blood and liver sterile.
51	4	None.	.....	One inoculation of 0.3 c.c. of bouillon-culture of staphylococcus aureus intravenously; no alcohol.	1170	920	+ (Abscesses in myocardium and muscles.)	0	Died four days after inoculation. *Autopsy:* Abscesses in myocardium and kidneys; none in voluntary muscles. No cultures.

EXPERIMENT VI.

Table showing results of subcutaneous inoculation of rabbits, receiving daily doses of ethyl-alcohol to the stage of intoxication, with cultures of staphylococcus aureus.

52	14	125	10–15	3 days; subcutaneous inoculation of 1 c.c. of a 24-hour bouillon-culture of staphylococcus aureus; 7 days later intravenous inoculation of 0.5 c.c. of similar culture.	1350	930	+ (Disseminated miliary abscess formation).	0	Died on fourteenth day—*i. e.*, eleven days after first and four days after second inoculation. ***Autopsy:*** Typical disseminated miliary abscess formations in muscles and internal viscera. No cultures.
53	6	55	7.5–10	3 days; one subcutaneous inoculation as above.	1380	1080	+ (Site of inoculation.)	0	Died on sixth day—*i. e.*, three days after inoculation. ***Autopsy:*** Small purulent mass at site of inoculation; no abscesses anywhere; large part of both lungs affected with pseudo-tuberculosis. ***Cultures:*** Staphylococcus aureus from site of inoculation. The slender bacillus referred to in protocol of Rabbit 48 obtained from lung.
				Controls.					
54	14	60 c.c. alcohol begun 7 days after 1st inocul'n—*i. e.*, with 2d inocul'n	10 c.c. for 6 days after second inoculation	7 days after first inoculation; first inoculat'n was 1 c.c. of a bouillon-culture of S. aureus subcutaneously; second was 0.5 of similar cultures intravenously.	2390	2080	+ (Abscesses in kidneys.)	+ (Stomach.)	Died on fourteenth day—*i. e.*, seven days after second inoculation. ***Autopsy:*** Post-mortem decomposition advanced; straw-colored fluid containing fibrin-like strands in pleural cavity; abscesses in kidneys; stomach injected. ***Cultures:*** Staphylococcus aureus from kidney, liver, and pleural cavity; bile, spleen, and peritoneum sterile.
55	8	No alcohol.	.....	First and second inoculations as above; no alcohol.	1940	1890	0	0	Died on day following last (second) inoculation. ***Autopsy:*** Beyond a slight distention of the pericardial sac with fluid, there were no lesions anywhere to be detected by the naked eye. No abscesses anywhere. ***Cultures:*** Staphylococcus aureus in moderate numbers from blood and kidney; pericardial sac sterile.

EXPERIMENT VII.

Table showing results of intraperitoneal inoculation of rabbits, receiving daily doses of ethyl-alcohol, with cultures of staphylococcus pyogenes aureus.

56	4	40	70	3 days; inoculated into peritoneum with 0.5 c.c. of 24-hour bouillon-cultures of S. aureus.	1050	880	0	0	Died on day following inoculation. ***Autopsy:*** Beyond a few c.c. of reddish fluid in peritoneum, there was no evidence of peritonitis. No other lesions. ***Cultures:*** Staphylococcus aureus in pure culture from peritoneum; blood and liver sterile.

Rabbits.	No. of days observed.	Total amount of alcohol received. C.c.	Daily dose of alcohol. C.c.	Interval between the beginning of alcohol and time of inoculation.	Weight in grammes. Beginning.	Weight in grammes. End.	Lesions referable to inoculations. + present. 0 = absent.	Lesions referable to the alcohol. + present. 0 = absent.	Results and remarks.
57	12	110	10	3 days, first inoculation as in No. 56, second inoculation on 7th day; intravenous injection of 0.5 c.c. of bouillon-culture of S. aureus.	1520	1430	0	0	Died two days after second inoculation. *Autopsy:* Small purulent nodule at point of puncture of first (intraperitoneal) inoculation; no peritonitis; pericardium roughened, but contained no bacteria microscopically; it had not the appearance of recent inflammation. Minute red points over the surface of kidneys; no abscesses detected anywhere. *Cultures:* A few colonies of staphylococcus aureus from blood and liver.
				Controls.					
58	3	...	....	No alcohol. Inoculated as No. 56.	.....	.....	0	0	Died on second day after inoculation. *Autopsy:* Ruptured uterus, with three dead fœtuses lying in abdominal cavity. *Cultures:* Blood sterile; staphylococcus aureus and short bacilli in peritoneal cavity.
59	16	...	.....	No alcohol. 7 days after the intraperitoneal inoculation an intravenous inoculation of 0.5 c.c. of bouillon-culture of S. aureus was given.	1000	870	+ (Abscesses in kidneys and in myocardium.)	0	Died nine days after second inoculation—*i. e.*, the intravenous injection. *Autopsy:* Kidneys and myocardium studded with abscesses; lung presented several caseous or suppurating nodules that contained cocci. *Cultures:* Staphylococcus aureus in liver, kidney, and bile.

Experiment VIII.

Table showing results of intravenous inoculation of rabbits, receiving alcohol daily to the stage of intoxication, with bouillon-cultures of staphylococcus pyogenes aureus.

60	2	12.5	12.5	Simultaneous, intravenous inoculation with 0.4 c.c. of a 24 hour bouillon culture of S. aureus.	.....	.....	+ (Heart and kidneys.)	+ (Stomach.)	Died on second day. *Autopsy:* Very delicate network of lymph over surface of heart; numerous very minute yellow points in kidneys; mucous membrane of stomach red and eroded. *Cultures:* Staphylococcus aureus in small numbers from blood, in very large numbers from kidney.

61	3	22.5	10–12.5	Same as No. 60.	1990	1860	+ (Myocardium, kidneys.)	+ (Stomach.)	Died on third day. *Autopsy:* Animal died as result of an accident. A small amount of alcohol was inspired into lungs; death followed at once. Several yellow points in myocardium, and numerous similar points in kidneys; none seen in voluntary muscles; mucous membrane of stomach very red and eroded over large part of its surface. *Cultures:* Blood sterile; kidneys gave staphylococcus aureus in very large numbers.
62	1	12.5	.....	Same as No. 60.	2000	.....	0	+ (Stomach.)	Died fifteen hours after inoculation. *Autopsy:* Entire cardiac two-thirds of stomach intensely reddened and mucous membrane eroded. *Cultures:* Blood sterile; kidney, four colonies of staphylococcus aureus.
63	2	22.5	10–12.5	Same as No. 60.	2050	.....	+ (Kidneys.)	+ (Stomach.)	Died forty-eight hours after inoculation. *Autopsy:* Conglomerate and single miliary abscesses in both kidneys; walls of stomach very much thickened, œdematous, and acutely reddened over about half its surface; stomach contained small amount of dark grumous material. *Cultures:* Blood sterile; kidney contained staphylococcus aureus.
64	1	12.5	.....	Same as No. 60.	1390	.....	+(?) (Pericardium.)	0	Found dead fifteen hours after inoculation. *Autopsy:* Pericardium filled with bloody serum; small amount of fluid in peritoneum. *Cultures:* Blood, twenty-one colonies; kidney, one colony of staphylococcus aureus.
65	1	12.5	.....	Same as No. 60.	1790	.....	0	+ (Stomach.)	Found dead fifteen hours after inoculation. *Autopsy:* Small amount of fluid in peritoneum; no peritonitis; mucous membrane of stomach red and eroded. *Cultures:* Staphylococcus aureus in blood and kidneys.

Controls—inoculated, but received no alcohol.

66	11	.....	.....	No alcohol. Inoculated as above.	2150	1530	+ (Abscesses in muscles, kidneys, and joint.)	.....	Died on twelfth day after inoculation. *Autopsy:* Numerous old abscesses in muscles, many almost as large as a pea; purulent suppuration about the joint of right hock; numerous old abscesses in kidneys; none in heart. *Cultures:* Staphylococcus aureus from kidney and suppurating joint. Blood sterile.
67	1	.....	.....	Same as No. 66.	2110	.....	0	.....	Died twenty hours after inoculation. *Autopsy:* Numerous extremely minute white points in myocardium; several pale, circumscribed, and also diffuse points in kidneys; mucous membrane of stomach normal. *Cultures:* Blood and kidneys sterile.
68	1	.....	.....	Same as No. 66.	1720	.....	+ (Heart, muscles, kidneys.)	.....	Died twenty-one hours after inoculation. *Autopsy:* Pericardium distended with serum; heart covered with a delicate network of fibrin; myocardium studded with minute pale points; voluntary muscles presented numerous small lens-shaped pale points; kidneys presented numerous pale areas that dipped into the cortex in a wedge shaped manner. *Cultures:* Staphylococcus aureus from kidney. Blood sterile.
69	36	.....	.....	Same as No. 66.	1730	.....	.....	.....	After forty-three days animal is apparently well; weighs 1560 grammes.

Rabbit's No.	No. of days alcohol served	Total amount of alcohol received (c.c.)	Daily dose of alcohol (c.c.)	Interval between the beginning of alcohol and time of inoculation.	Weight in grammes. Beginning	Weight in grammes. End.	Lesions referable to inoculations. + present. 0 absent.	Lesions referable to the alcohol. + present. 0 absent.	Results and remarks.
70	1			Same as No. 69.	1350	.....	+ (?) (Pericardium.)	.....	Died twenty hours after inoculation. *Autopsy:* Pericardium filled with serum, in which was a colorless clot and a few strands of fibrin; diffuse pale areas in cortex of kidneys. *Cultures:* Blood, one colony of staphylococcus aureus; kidney sterile.
71	4			Same as No. 69.	1970	1780	+ (Abscesses in heart, kidneys, and muscles.)	....	Died on fifth day after inoculation. *Autopsy:* On inner aspect of left thigh was a collection of pus about the size of a chestnut; numerous abscesses in muscles; several abscesses in myocardium; numerous abscesses in both kidneys; small area of peritonitis in left iliac region. *Cultures:* Staphylococcus aureus from blood, kidney, and abscess in thigh.

EXPERIMENT IX.

Table showing results of subcutaneous inoculation of rabbits, receiving alcohol to the stage of intoxication daily, with cultures of staphylococcus pyogenes aureus.

72	11	55	5	Simultaneous. Subcutaneous inoculation of 1 c.c. of a bouillon-culture of S. aureus.	2520	2140	+ (Site of inoculation.)	0	Died on twelfth day after inoculation. *Autopsy:* At site of inoculation in the left groin the tissues were dissected apart, leaving a moderately large excavation; this contained neither serum nor pus. About the borders of this the tissues were very odematous, the œdema extending up into the neck and into the thighs of both sides. Middle lobe of right lung consolidated. *Cultures:* Staphylococcus aureus from blood, from site of inoculation in large numbers, and from kidney; lung also contained them, but associated with a short bacillus.
73	14	75	5 10	Same as No. 72.	1690	1460	+ (?) (Pericarditis and pleuritis.)	0	Died on fifteenth day after inoculation. *Autopsy:* A trace of suppuration only at site of inoculation; fibrino-purulent pleuritis and pericarditis; moderate amount of blood-stained purulent matter in pleural cavities. *Cultures:* From pleural cavity a feebly growing staphylococcus was obtained. Cannot say that it was or was not staphylococcus aureus.
74	5	30	5 10	Same as No. 72.	1720	1400	+ (?) (Pericarditis and pleuritis.)	0	Died on fifth day as direct result of last dose of alcohol, from under the influence of which it did not recover; animal was very susceptible to alcohol. By mistake its last dose was 10 c.c. instead of 5 c.c., as had been the case. *Autopsy:* Slight purulent reaction at site of inoculation; purulent pericarditis and pleuritis; no abscesses; slight peritonitis. *Cultures:* Blood, left pleura, kidney, and spleen gave a feebly growing staphylococcus identical to that found in No. 73. Site of inoculation gave typical staphylococcus aureus.

75	1	10	.....	Same as No. 72.	1590	.....	0	0	Died during night of day of inoculation. *Autopsy:* No macroscopic lesions anywhere to account for death; stomach normal and filled with partly digested food. *Cultures:* Staphylococcus aureus from site of inoculation; blood and kidney sterile.
76	14	140	10	Same as No. 72.	2420	2050	+(?) (Pericarditis and pleuritis.)	0	Died on fifteenth day after inoculation. *Autopsy:* At site of inoculation was circumscribed collection of cheesy pus of about size of an almond; fibrino-purulent pericarditis and pleuritis; both thoracic cavities filled with purulent matter. *Cultures:* Staphylococcus aureus in large numbers from the site of inoculation; a few colonies of cocci from liver. Thoracic cavity gave large numbers of slowly growing micrococci that gave the impression of an enfeebled culture of staphylococcus aureus (see Nos. 73 and 74).
77	9	90	10	Same as No 72.	1660	1260	0	0	Died on tenth day after inoculation. *Autopsy:* Only slight reaction at site of inoculation; no lesions on macroscopic examination to account for death. *Cultures:* Blood, liver, and kidney sterile.
						Controls.			
78	46	.....	.....	No alcohol. Inoculated as above.	2130	.....	0	.....	Apparently well after forty-six days; weighs 1850 grammes.
79	46	.....	.....		1560	.....	0	.....	Apparently well after forty-six days; weighs 1780 grammes.
80	46	.....	.....		1490	.....	0	.....	Apparently well after forty-six days; weighs 1570 grammes.

EXPERIMENT X.

Table showing results of subcutaneous inoculation of rabbits, receiving daily doses of ethyl-alcohol to the stage of intoxication, with cultures of staphylococcus pyogenes aureus, attenuated (?) by exposure to chloroform.

81	7	45	5–7.5	2 days; intravenous inoculation with 0.6 c.c. of a chloroformed culture of S. aureus.	1200	1050	+ (Pelvis of kidney; thoracic cavity(?).)	+ (Stomach.)	Died on fifth day after inoculation. *Autopsy:* Pleural cavities and pericardium filled with clear serum; purulent inflammation of pelvis of right kidney; no cortical lesions; urine contained microscopically numerous micrococci; mucous membrane of stomach eroded. *Cultures:* Blood, left kidney, peritoneum, and liver sterile; pelvis of right kidney and urine contained staphylococcus aureus in large numbers.
82	4	22.5	5–7.5	Same as No. 81.	1630	1640	+(?) (Peritonitis.)	+ (Stomach.)	Died on second day after inoculation. *Autopsy:* General acute peritonitis, with deposit of lymph over coils of intestines; mucous membrane of stomach very red and eroded. *Cultures:* Blood, kidney, and peritoneum all contained a pure culture of a staphylococcus that grew slowly and suggested an attenuated staphylococcus aureus.
						Controls.			
83	28	.....	.....	No alcohol. Inoculated as above.	1350	1530	.....	.....	The observation was discontinued at twenty-eighth day. The animals had gained in weight, and had at no time shown effects of the treatment.
84					1410	1750			

Conclusions.

The deductions that may be drawn from the results of these experiments are as follows:

That the normal vital resistance of rabbits to infection by streptococcus pyogenes (erysipelatis) is markedly diminished through the influence of alcohol when given daily to the stage of acute intoxication. That a similar, though by no means so conspicuous, diminution of resistance to infection and intoxication by the bacillus coli communis also occurs in rabbits subjected to the same influences. And that, while in alcoholized rabbits inoculated in various ways with staphylococcus pyogenes aureus, individual instances of lowered resistance are observed, still it is impossible to say from these experiments that in general a marked difference is noticed between alcoholized and non-alcoholized animals as regards infection by this particular organism.

It is interesting to note that the results of inoculation of alcoholized rabbits with the erysipelas coccus correspond in a way with clinical observations on human beings addicted to the excessive use of alcohol when infected by this organism.

In the course of the work an effort was made to determine if, through the oxidation of alcohol in the tissues to acids of the corresponding chemical group, the increase of susceptibility could be referred to a diminution in the alkalinity of the blood as a result of the presence of such acids. The number of experiments thus far made on this point is too small to justify dogmatic statements, but from what we have gathered there is but little evidence in support of this view.

Throughout these experiments, with few exceptions, it will be seen that the alcoholized animals not only showed the effects of the inoculations earlier than did the non-alcoholized rabbits, but in the case of the streptococcus inoculations the lesions produced (formation of miliary abscesses) were much more pronounced than are those that usually follow inoculation with this organism.

With regard to the predisposing influence of the alcohol, one is constrained to believe that it is in most cases the result of structural alterations consequent upon its direct action on the tissues, though in a number of the animals no such alteration could be made out by

macroscopic examination. I am inclined, however, to the belief, in the light of the work of Berkley and of Friedenwald, done under the direction of Prof. Welch, in the Pathological Laboratory of the Johns Hopkins University, that a closer study of the tissues of these animals would have revealed in all of them structural changes of such a nature as to indicate disturbances of important vital functions of sufficient gravity to fully account for the loss of normal resistance.

The conspicuous influence of the alcohol on the gastric mucous membrane in many of these animals, with the consequent disturbance of nutrition, is undoubtedly the explanation of the marked loss in body weight that was observed in many of the animals employed in these experiments. In this light the susceptibility induced by alcohol to excess is somewhat analogous to that induced by starvation, where we see the resistance of animals to particular forms of infection very markedly diminished.

DISCUSSION.

DR. MELTZER: I would like to ask Dr. Abbott if he used alcohol by the mouth exclusively, or if he also used it hypodermically, or by the rectum.

DR. A. C. ABBOTT: The primary object of my experiment was to make the conditions somewhat similar to those associated with the drinking of alcohol. However, under the second head of the paper, "The Effect of Chronic Alcoholism," I had it in mind to try giving the alcohol through the rectum, as the repeated passage of the stomach-tube gives rise to such irritation as to render it improbable that this method would be suitable for the production of chronic alcoholism.

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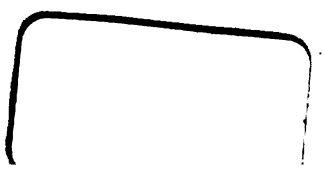
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